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The Journal of Pediatrics

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CEPHALHEMATOMA ASSOCIATED WITH FRACTURE OF THE SKULL

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CEPHALHEMATOMA in newborn infants results from an accumulation of blood beneath the periosteum of the skull. Fractures of the underlying bone have rarely been recognized. In a review of the literature on cephalhematomas in which reference is made to roentgenographic studies,[1, 2] the only reference to associated fractures of the skull was by Caffey,[3] in the second edition of his book. He states, "The usual cause is trauma to the fetal head during labor and hemorrhagic disease may be an added predisposing causal factor. Fine linear fractures of the underlying bone are often found in the sites of cephalhematoma and are thought by some to be the principal cause of bleeding under the pericranium." No references or statistics are given.

The present study to determine the incidence of fracture of the skull in infants with cephalhematomas was undertaken following the roentgenographic demonstration of a fracture of the parietal bone underlying a cephalhematoma in a newborn infant. An attempt has also been made to evaluate possible etiological factors.

METHOD OF STUDY

From March 1, 1949, to May 31, 1950, all infants born at Temple University Hospital were examined for the presence or absence of cephalhematoma. During the fifteen-month period, 2,774 infants were delivered; 1,568 were on the private or semiprivate service and 1,206 were on the ward service. During the period of study, vitamin K was not administered to the mothers or to the infants as a routine measure. All infants were examined by the pediatric resident physician during the first twenty-four hours of life and upon discharge from the hospital. All infants with a cephalhematoma were examined by one of us (N. K.), and roentgenographic examinations of the skull were obtained.

The initial roentgenographic studies consisted of three stereoscopic views of the skull: anteroposterior (fronto-occipital), anteroposterior (30° fronto-occipital), and lateral (side of the swelling) exposures. Bucky screen technique was employed. Factors employed were 60 kv. for the anteroposterior projection and 55 kv. for the lateral projection, 100 ma., and 1/5 second at a distance of 46 inches. Immobilization was obtained by placing the infant between two sandbags and by using a head clamp. The final seventeen examinations were made with single fronto-occipital, single 30° fronto-occipital, stereolateral (side of the cephalhematoma) and single tangential views. Cardboard technique

From the Departments of Pediatrics and Radiology, Temple University School of Medicine.

Fig. 1.—Linear fracture of parietal bone underlying soft tissue swelling representing cephalhematoma.

Fig. 2.—Lateral projection of skull demonstrating linear fracture in posterior portion of parietal bone.

was employed for the tangential view; the factors employed were 70 kv., 100 ma., and ¼ second at a distance of 30 inches.

RESULTS

Incidence.—Cephalhematomas were observed in sixty-nine of the 2,774 newborn infants, an incidence of 2.49 per cent. Roentgenographic examinations of the skulls were obtained in sixty-four of the infants; in two instances the examinations were not obtained because of the death of the infants and in three instances because of errors of omission. Of the sixty-four infants with cephalhematomas examined roentgenographically, sixteen, or 25 per cent, were found to have a fracture of the parietal bone at the site of the cephalhematoma. In each instance the fracture was observed on the lateral projection; only rarely did the anteroposterior or tangenital view reveal it. The fracture lines as illustrated in Figs. 1 and 2 were linear in type; they extended into the parietal bone from the midsagittal suture, approximately at a right angle to this suture. The irregular ossification pattern of the posterior half of the parietal bone as seen on the lateral projection was recognized and was not misinterpreted as a fracture.

Etiological Factors.—Of the sixty-nine infants with cephalhematomas, forty-two, or 61 per cent, were males and twenty-seven, or 39 per cent, were females. Of those with fractures of the skull, nine were males, and seven females; eleven were on the private service, and five were on the ward service. Other studies[1, 4, 5] also revealed that cephalhematomas are more common in male infants. No adequate explanation is available for this difference in the two sexes. Fifty-seven, or 83 per cent, of the cephalhematomas occurred in infants on the private service, whereas twelve, or 17 per cent, were in infants on the ward service. Of the total number of 2,774 infants delivered, 1,568, or 56.5 per cent, were on the private service and 1,206, or 43.5 per cent, were on the ward service. The higher incidence of cephalhematomas on the private service in contrast with that on the ward service is statistically significant. Though there is inadequate evidence to explain this disproportion, the possibility that it may be related to differences in obstetric practices must be considered.

Table I. Site of Cephalhematoma and Fracture

Site of Cephalhematoma	Number	Site of Fracture	
		Right	Left
Right Parietal	40	8	0
Left Parietal	17	0	5
Bilateral Partietal	11	1	2
Occipital	1	0	0
Totals	69	9	7

As shown in Table I, forty, or approximately 60 per cent, of the cephalhematomas occurred over the right parietal bone, seventeen over the left parietal bone, and in eleven instances both parietal bones were involved. The greater number of cephalhematomas occurring over the right parietal region is in accord with published reports.[1, 4] The infant with the cephalhematoma of the occipital bone was a breech presentation. In each instance of unilateral cephalhematoma, the fracture occurred

in the parietal bone involved, whereas in the three instances of bilateral cephalhematomas the fracture occurred twice on the left and once on the right side. No relation could be established betwen the size of the cephalhematoma and the presence or absence of a fracture.

As shown in Table II, approximately 75 per cent of the infants born during the period of observation were delivered with forceps, in contrast to sixty-four, or 93 per cent, of the group with cephalhematomas being delivered with forceps; this disproportion is statistically significant. Three of the infants with cephalhematomas were delivered by cesarean section and one as a breech presentation. In two of the cesarean sections, the head was delivered with Allis forceps and the cephalhematomas occurred at the sites of application. It may be that mechanical trauma was the causative factor in these two instances. In only one instance was the delivery of an infant with a cephalhematoma spontaneous. Thus it may be that the high incidence of cephalhematomas in our series is related in some way to the mechanical assistance delivery. Ingram and Hamilton[1] also observed a greater percentage of cephalhematomas among infants delivered with forceps than in those who were delivered spontaneously. As stated previously, 82 per cent of the cephalhematomas occurred among the private patients who accounted for only 56.5 per cent of the deliveries. Approximately 81 per cent of the deliveries on the private service were with forceps in contrast to 65 per cent on the ward service. This disproportion is statistically significant.

TABLE II. RELATIONSHIP OF CEPHALHEMATOMA WITH AND WITHOUT A FRACTURE OF THE SKULL TO THE TYPE OF DELIVERY

TYPE OF DELIVERY	ENTIRE GROUP		CEPHALHEMATOMA		CEPHALHEMATOMA WITH FRACTURE	
	NO.	%	NO.	%	NO.	%
Forceps	2,090	75.3	64	92.8	15	93.8
Spontaneous	551	19.9	1	1.4	0	0.0
Cesarean	110	4.0	3	4.4	1	6.2
Breech	15	0.5	1	1.4	0	0.0
Version	8	0.3	0	0.0	0	0.0
Totals	2,774		69		16	

TABLE III. RELATIONSHIP OF PARITY OF MOTHERS TO THE INCIDENCE OF CEPHALHEMATOMAS

	ENTIRE GROUP		CEPHALHEMATOMA		CEPHALHEMATOMA WITH FRACTURE	
	NO.	%	NO.	%	NO.	%
Primipara	1,044	38.2	51	73	14	88
Multipara	1,690	61.8	18	27	2	12

Table III shows the incidence of cephalhematomas with and without a fracture in relation to parity of the mothers. In fifty-one instances the mothers of infants with cephalhematomas were primiparas and in eighteen instances they were multiparas. Skull fractures occurred in fourteen infants of primiparas and in two of multiparas. Thus, approximately 73 per cent of the cephalhematomas occurred in infants of primiparas who as a group comprised only 38.2 per cent of the total number, a fact which has statisti-

cal significance. A greater incidence of cephalhematomas among infants of primiparas has also been noted by Oshima[5] (74 per cent), by Sjöval[4] (70 per cent), and by Ingram and Hamilton.[1]

The ages of the mothers of infants with cephalhematomas varied from 17 to 36 years. The greater incidence was in infants born of mothers ranging in age from 22 to 29 years. There is no apparent relationship of the incidence of cephalhematomas with or without fractures of the skull to the age of the mothers.

DISCUSSION

The development of a cephalhematoma is probably secondary to rupture of blood vessels which traverse from the skull to its periosteum. Repeated traumatic contact of the infant's skull against the maternal pelvis during labor and the use of forceps in delivery would appear to be the principal opportunities for adequate injury. The tumor mass is usually located over one of the parietal bones and never extends across the suture lines, the hemorrhage being limited by the periosteum at the periphery of the involved bone. Oshima[5] states that the periosteum of the skull is separated along the tangential plane of the presenting part and found that in 60 per cent of the cases a complication of labor was present. According to Naujoks[6] the local pressure and tangential force are the effective etiological factors. Hartley and Burnett[2] suggest that trauma of a dragging nature is the precipitating factor but that defective development of the vault bones and hypoprothrombinemia may be contributory factors.

Available data indicate that cephalhematomas occur relatively frequently in newborn infants, though the incidence of 2.49 per cent in our series is high in comparison to other published data. Ingram and Hamilton[1] found an incidence of 1.66 per cent; Kastendieck,[7] 1 per cent; and Sjöval[4] reported 171 cases among 40,252 deliveries, an incidence of 0.41 per cent.

In the attempt to explain the relatively high incidence of cephalhematomas in our series, the possibility that some of them may have been related to the use of forceps must be considered in view of the significantly higher incidence of deliveries with forceps on the private service in contrast to that on the ward service. Fifteen of the sixteen infants with a fracture of the skull were delivered with forceps. Thirteen of them were delivered by low or outlet forceps with or without an episiotomy. These deliveries consisted only of lifting the fetal head over the perineum after it had been rotated to an anterior position and was visible at the introitus. In only one instance was forceps rotation from a posterior position performed and in another, delivery by midforceps extraction was necessary. Since all but two of the fractures of the skull were associated with simple forceps deliveries which have been shown not to increase fetal mortality, it does not seem likely that the single factor of forceps trauma is the only causal effect, nor is there evidence that it is the most frequent one. The reputed higher incidence of contraction of the lower pelvis among private patients in contrast to that among ward ones must also be taken into account. The delay in the terminal phase of labor in women with such contractions may itself permit for prolonged

Fig. 3.—Fracture of left parietal bone demonstrated at autopsy. The fracture line runs perpendicular to and from the sagittal suture to the periphery of cephalhematoma.

Fig. 4.—Huge cephalhematoma measuring 30 cm. in circumference at the base. The infant required transfusions for correction of an anemia.

and repeated trauma to the infant's head. Whether the failure to administer vitamin K to the infants was a factor is not known; however, Ingram and Hamilton[1] found no difference in the incidence of cephalhematomas in infants born to mothers who received vitamin K as compared to a control group in which they did not receive it.

In no instance did an infant with a fracture of the skull have symptoms referrable to the central nervous system. The behavior of these infants was not abnormal during their stay in the nursery. Five of the sixteen infants with a fracture of the skull were examined on several occasions during their first year of life. None of them exhibited untoward effects, and their growth and development patterns were within normal limits.

Since this series was completed, an additional cephalhematoma with an underlying fracture of the parietal bone was observed at autopsy in a premature infant who died at the age of 72 hours (Fig. 3). In addition to the fracture of the skull, bilateral, subdural, and intracranial hemorrhages were also present.

Other complications of cephalhematoma are infrequent. Cohen and associates[8] reported an instance of cephalhematoma with secondary infection terminating in purulent meningitis; one of us (N. K.) has seen a similar case.

One of our infants with bilateral cephalhematomas had a cerebral hemorrhage, but roentgenographic examination failed to reveal any evidence of a fracture of the skull. The tumor over the right parietal bone was approximately the size of a fetal head (Fig. 4). The hemorrhage was sufficiently extensive to require transfusions of blood to correct the anemia. Kosmak[9] reported a similar case.

Calcification of cephalhematomas occurs frequently, and following the absorption of blood, a calcified ridge may be present at the periphery. This is usually absorbed eventually, though bony deformities of the skull have been reported as a permanent complication of cephalhematomas. Ottow[10] reported an instance of a bony cyst formation following a cephalhematoma. Chorobski and Davis[11] operated upon a 7-week-old infant with an occipital cephalhematoma. The mass had been present since birth, and at operation a thin eggshell-like layer of bone was found to overlay a multilocular cyst containing thick, brownish, syruplike fluid. The same authors quote reports of other cases of cephalhematomas with permanent cranial deformities.

Therapeutic measures are rarely necessary for cephalhematomas. Morgan[12] advised aspiration of the tumefaction if absorption of the blood did not occur by the second week. Kastendieck,[7] however, states that the blood should never be aspirated, a policy which is now generally recommended. In our series, treatment directed to the cephalhematoma was found to be unnecessary.

SUMMARY

In a series of 2,774 newborn infants observed over a period of fifteen months, sixty-nine, or 2.49 per cent, of them had a cephalhematoma. Of the sixty-four infants who were examined roentgenographically, sixteen, or 25 per cent, had a fracture of the parietal bone underlying the cephalhematoma.

In only one instance were symptoms other than the tumefaction observed;

these were the result of an associated intracranial hemorrhage. This infant, with a cephalhematoma sufficiently large to produce an anemia, required transfusions of blood.

The incidence of cephalhematomas would seem to be greater over the right parietal bone than over the left one and more common in male than in female infants.

Statistical analysis of the data revealed that cephalhematomas, with or without a fracture of the skull, occurred more often in infants born of primiparous women, with the incidence being higher in infants delivered with forceps than in those delivered spontaneously.

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HEMORRHAGIC INFARCTION OF THE KIDNEYS IN INFANTS

Report of a Unilateral Case in an 8-Day-Old Male Infant With Survival of Infant Following Successful Nephrectomy

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A REVIEW of the literature indicates that until June, 1950, successful nephrectomy for hemorrhagic infarction of the kidney in an infant, followed by survival of the infant, has been reported in only three instances. Campbell and Matthews[1] reported two such cases in 1942, and Sandblom[2] the other in 1948. Our patient is believed to be the fourth one to survive following surgery. This case is unusual in that the correct diagnosis was made preoperatively from the presenting clinical features.

CASE REPORT

D. G., a white male infant, was admitted to Letterman Army Hospital on Nov. 14, 1949, at the age of 8 days. The chief complaints were fever, vomiting, abdominal distention, and oliguria of two days' duration. His delivery on November 6 at the Hamilton Air Force Base Hospital, California, was said to have been uneventful. The birth weight was 8 pounds 13½ ounces, which he regained by the fifth day of life on an artificial milk formula. He was considered to be a normal newborn infant until the sixth day of life, when he developed a fever of 104° F. without any discernible cause. The next day he began to vomit copious quantities of greenish clear fluid associated with abdominal distention. Although he passed some urine, a rather marked oliguria was noted to be present.

On admission, he appeared to be critically ill and was moderately dehydrated. Respirations were rapid and deep. Two indurated masses, each about 2 cm. in diameter and about ½ cm. above the surface, were present on the parietal areas of the scalp. The abdomen was distended, tense, tympanitic, and "silent" to auscultation. The liver edge was palpable 2½ cm. below the costal margin and the spleen could be outlined 2 cm. below the left costal margin. The most remarkable finding was the palpation of a smooth, firm, 3 × 6 cm. mass in the right lower quadrant of the abdomen which extended into the right flank in the same location as the right kidney.

The erythrocyte count was 3.7 million per cubic millimeter; hemoglobin 11.4 Gm.; leukocyte count 10,300 per cubic millimeter, with normal differential count for age; platelets 308,000; clotting time 3 min., and bleeding time 1½ min. Catheterized urine revealed 4 plus albumin, acid reaction, trace of sugar, and 2 plus positive benzidine test. Microscopic examination of the urine sediment revealed 1 to 3 granular casts, 5 to 8 red blood cells, and 8 to 12 white blood cells per high-power field. Numerous bacteria were noted on the stained smear which later proved to be nonhemolytic *Staphylococcus aureus* by culture. Blood carbon dioxide combining power on admission was 7.4 meq. per liter, and the blood nonprotein nitrogen was 55 mg. per cent. Cultures of the blood and scalp ulcer revealed hemolytic *Staph. aureus* and nonhemolytic *Staph. aureus*, respectively. Intravenous pyelographic studies were unsatisfactory in that the dye did not appear in either kidney. Diodrast dye, injected into the bladder, revealed a normal-sized bladder and a dilated right ureter. The findings of a flat-plate x-ray of the abdomen were interpreted to

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be consistent with adynamic ileus. A mechanical intestinal obstruction was not believed to be present.

The clinical and laboratory findings indicated the infant had developed sepsis, with resultant fever, vomiting, dehydration, metabolic acidosis, and abdominal distention on the sixth and seventh days of life. On the eighth day of life, hemorrhagic infarction and/or renal vein thrombosis of the right kidney was believed to have occurred, as evidenced by oliguria, azotemia, a palpable, enlarged right kidney, and the abnormal urine findings of albuminuria, hematuria, pyuria, and cylindruria. After correction of the dehydration and metabolic acidosis by parenteral fluids and whole blood through a cutdown of an ankle vein, the infant was taken to surgery twenty-four hours after admission on November 15. The preoperative diagnosis was hemorrhagic infarction and/or renal vein thrombosis of the right kidney. A right nephrectomy, through a right flank incision, was successfully carried out.

Pathological Report on Removed Right Kidney.—Grossly, the kidney weighed 50 grams (normal, 15 grams) and measured 6 × 3.5 × 3 cm. The capsule was taut. The renal surface was coarsely lobulated and generally had a deep violaceous surface with mottled areas of irregular diffuse light tan to dark gray discolorations (Fig. 1). When the kidney was sectioned (Fig. 2), a moderate amount of blood exuded from the bulging sectioned surfaces. The capsule stripped with difficulty because of extreme friability of the renal parenchyma. There was faint retention of renal architecture. The cortex was extremely soft, reddish brown, and measured 4 mm. in its least depth in areas where is could be distinguished. In many areas, the medullary and cortical zones were quite indistinct and the parenchyma was

Fig. 1.

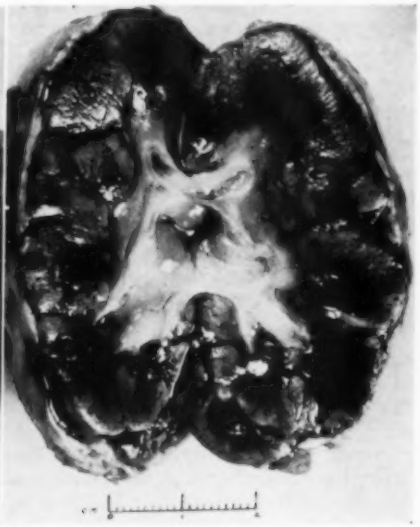

Fig. 2.

Fig. 1.—Kidney, gross unsectioned. Weight 50 grams; measurement 6 x 3.5 x 3 cm.; capsule taut, renal surface lobulated, deep violaceous color with mottled areas of irregular diffuse light tan to dark gray discolorations.

Fig. 2.—Kidney, gross sectioned. Large amount of blood exuded when sectioned.

largely replaced by hemorrhagic necrotic tissue. There was no ectasia of the calyces and the wall of the pelvis presented a smooth, light gray, glistening surface.

Microscopic sections of the kidney showed the majority of it to be infarcted, with only shadows of the former structure remaining. Degenerative changes varied considerably, progressing from interstitial hemorrhage to mild necrosis to complete destruction of the parenchyma (Figs. 3 and 4). Thrombi were not demonstrated in the lumen of interlobar, arcuate, or interlobular vessels. No vascular pathology could be demonstrated. The renal pelvis and calyces generally

Fig. 3.

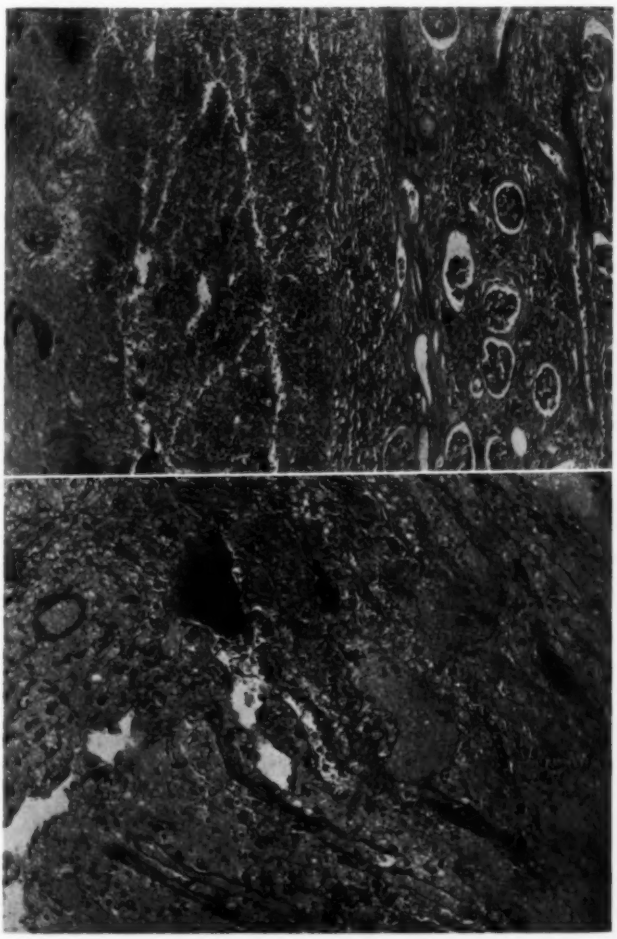

Fig. 4.

Fig. 3.—Completely infarcted with zone of necrotic tissue adjacent to which there is kidney showing interstitial hemorrhage and possibly early infarction.

Fig. 4.—High-power view. Completely infarcted kidney showing only ghost forms of previous architecture.

showed no changes. The pathological diagnosis was hemorrhagic infarction, without renal thrombosis, of the right kidney.

Postoperative Course.—This was stormy for the first two weeks. During this period, required parental fluids, whole blood, and antibiotics were given. A moderate icterus, hemolytic in type, developed on the second day. Renal insufficiency, indicated by oliguria and anuria, azotemia, and abnormalities of the urine sediment persisted for six days. Renal function and the urine then returned to normal. Metastatic skin abscesses developed on the tenth day, associated with persistent positive blood cultures for hemolytic *Staph. aureus*, in spite of intensive penicillin and streptomycin therapy. Sulfadiazine therapy was started after in vitro tests revealed the organisms were insensitive to penicillin and streptomycin but sensitive to sulfadiazine. The blood cultures then became negative and the skin abscesses disappeared. Retrograde pyelograms showed a normal genitourinary system except for the absence of the right kidney and a dilated right ureteral stump.

The infant made a complete recovery and was discharged to his home on the thirty-fourth hospital day following surgery. At 3 months of age, he weighed 13 pounds 8 ounces. The blood count, urinalysis, and blood chemistries were normal at this time. At 4 months of age, he weighed 16 pounds 7 ounces. At this time examination revealed bilateral cataracts of the eyes, believed to have been caused by his past illness. At 6 and 8½ months of age, during hospitalization for eye surgery, he developed urinary infections caused by *Escherichia coli* and *Pseudomonas aeruginosa* organisms. Both attacks responded well to sulfadiazine therapy. The urinary infections were believed to be incidental to empyema of the right ureteral stump which remained following surgery. Prior to nephrectomy, urographic studies had revealed a right congenital hydroureter, which probably was also a predisposing factor. After his last hospitalization at 8½ months, he was to have been brought back to the hospital after one month for possible removal of the right ureteral stump, and eye surgery. However, the parents failed to return him, and the family has now moved away to another part of the country. When the infant was last seen at 8½ months of age, growth and development were normal, and except for the cataracts of the eyes, he was a healthy baby, without any evidence of renal damage or dysfunction.

Comments.—A preoperative diagnosis of hemorrhagic infarction of the right kidney was made, based on the findings of oliguria, hematuria, and the appearance of a firm, smooth renal mass in the right side during the course of an acute infectious illness (hemolytic *Staph. aureus* sepsis), associated with vomiting, dehydration, metabolic acidosis, and shock. Prompt nephrectomy, within twenty-four hours following the appearance of the renal mass, saved this infant's life. The oliguria and azotemia which persisted following the nephrectomy was believed by us to have been due to the occurrence of lower nephron nephrosis in the remaining left kidney. Certainly, the basis for this type of lesion was present in that there was shock and blood destruction with increase in blood pigment. The state of oliguria and uremia persisted for six days, which then cleared up after this period of time. This time interval is characteristic for those cases of lower nephron nephrosis that recover.

The causal relationship of the existing right congenital hydroureter to the renal infarction is interesting. It is our opinion that it was only an incidental finding and that it had no causal relationship to the renal infarction. Our opinion is based on the fact that the pathological studies of the removed kidney failed to show inflammation of, or suppuration of, the pelvis or calyces that would have developed if there had been pyelonephritis from ureteral urinary obstruction.

DISCUSSION

Hemorrhagic infarction of the kidneys is an extremely grave disease and is generally fatal. When there is bilateral involvement, it is almost invariably fatal. However, Fallon[3] described the case of a newborn infant in which the clinical diagnosis of bilateral renal thrombosis and hemorrhagic infarction was made, with recovery of the infant without surgery. When hemorrhagic infarction is unilateral, the prognosis is much more favorable, provided that nephrectomy is performed early and immediately. Campbell and Matthews[1] state that about 75 per cent of patients with unilateral involvement may be expected to survive if prompt nephrectomy is employed, and the infant is not hopelessly septic.

Involvement of the kidneys with hemorrhagic infarction in infancy, and childhood is not a common condition. Kobernick and associates[4] state that most figures place the incidence at lower than 1.0 per cent in terms of total necropsies performed. A review of the literature[5, 6, 7] indicates that only 258 cases, including the present one, have been reported. About half the cases are unilateral with no preference for either side. Sex incidence is about equal.

Ante-mortem diagnosis of this condition is rare. It now seems apparent that the clinical picture is sufficiently clear that ante-mortem diagnoses should be made in the majority of cases. It is hoped that the present communication serves to emphasize to all physicians the urgency of early recognition of this disease entity so that prompt employment of nephrectomy in unilateral cases is undertaken as a life-saving measure. The time element is important. If the condition is not recognized early and nephrectomy performed in a period measured in terms of hours or several days, the infant will expire. Death results from uremia, either from involvement of the opposite kidney by extension of the thrombus from the initially involved kidney through the vena cava to the opposite renal veins, or from renal failure caused by the thrombotic and/or infarcted kidney on the one side and insufficiency of the kidney on the other side, most probably from lower nephron nephrosis.

The predisposing initial illness of infection, diarrhea, acidosis, dehydration, and shock may well mask the subsequent occurrence of renal infarction and thrombosis if a search is not made for the disease. A plea is made to physicians to frequently note the urinary output, to examine the urine, and to perform frequent abdominal examinations for the detection of renal masses in infants ill with infection, diarrhea, dehydration, and shock. It is only by a high index of suspicion and subsequent vigil for this disease that infants with unilateral renal infarction and thrombosis will be saved by the employment of prompt nephrectomy.

Etiology and Pathogenesis.—Hemorrhagic infarction of the kidneys may occur either alone without thrombosis of renal veins, or it may occur associated with thrombosis. And then, thrombosis of the renal veins may occur alone without hemorrhagic infarction. These varied pathological patterns are of main interest to the pathologist. To the clinician, it is only important to recognize the one clinical picture produced by hemorrhagic infarction and renal vein thrombosis to-

gether, or either alone, so that prompt and early nephrectomy may be employed in unilateral cases.

The following classification is proposed, based on the reports of various authors[8, 9, 10, 11] and our own experience.

1. Primary thrombosis of renal veins.
   a. Without infarction.
   b. With infarction.
2. Primary hemorrhagic infarction of the kidney without renal vein thrombosis.
3. Infarction secondary to renal inflammation with or without venous thrombosis.

The secondary variety develops as an extension of phlebitis of the vena cava, ureteral, ovarian, spermatic, and suprarenal vessels, or follows pronounced renal inflammation such as acute suppurative pyelonephritis.

In the primary groups, the disease seems to be due to a combination of *inherent* predisposing factors and *acquired* predisposing factors. The inherent predisposing factors are: (1) A precarious water balance in early infancy in favor of dehydration and increased viscosity of the blood[12]; (2) the anatomical nature of the renal circulation with its double capillary network with a natural slowing of the blood stream in the kidneys[13]; (3) the low arterial, capillary, and venous pressures in infancy[14]; (4) the predominant status of bedrest in infants, causing increased coagulability of the blood due to increased amounts of circulatory thromboplastin[15]; (5) possible bleeding tendency due to low blood prothrombin levels in neonatal period.[1, 4] The acquired predisposing factors are: (1) Dehydration from any cause, mainly diarrhea and/or vomiting; (2) infection elsewhere in the body than in the kidneys; (3) shock; (4) widely used therapeutic agents as penicillin and streptomycin.[16]

It can be recognized that the above predisposing factors, especially when in combination to enhance one another, represent known components which produce intravascular thrombosis, increased coagulation and viscosity of the blood and infarction. Macht has reported the thromboplastic properties of penicillin and streptomycin in animals.

Koberniek and associates[4] have made a study of the sites of predilection of renal thrombosis and infarction. The common sites are the smaller veins, arcuate and interlobular, and in the region of the corticomedullary junction.

It is not exactly clear why in one case hemorrhagic infarction occurs alone without renal thrombosis, in another, renal thrombosis without infarction, and in others, both infarction and thrombosis. Zuelzer[7] is of the opinion that there is a common factor which produces either or both hemorrhagic infarction or renal vein thrombosis. He states that this common factor is *stasis* and that it is the degree of completeness and suddenness of the stasis that determines one or the other, or both. Perhaps when stasis is gradual, hemorrhagic infarction without thrombosis occurs, due to anoxia to the capillary walls, with diapedesis of cells, followed by frank interstitial hemorrhage.

In unilateral cases involved with hemorrhagic infarction with or without vascular thrombosis, there is evidence that the opposite kidney may be involved with lower nephron nephrosis. In one of the fatal cases reported by McClelland and Hughes,[5] typical

renal vein thrombosis with hemorrhagic infarction was found in one kidney, whereas the other kidney demonstrated only the findings of lower nephron nephrosis. It is not surprising that this lesion may occur in these infants, as the two basic causes of lower nephron nephrosis mentioned by Mallory, namely, shock and increased blood pigment excretion, are present. Death of the infant may result on this basis.

Diagnosis.—In the usual case, more often in the neonatal period, there is a definite sequence of events. The previously healthy infant develops an infection (omphalitis, dermatitis, pneumonia, otitis media, sepsis, iliocolitis, or any type). Diarrhea and/or vomiting ensues with the development of dehydration, metabolic acidosis, and shock. After a period, usually of from one to four days, findings related to the urinary system occur. These are oliguria or anuria, hematuria and/or hemoglobinuria, albuminuria, and mild pyuria, associated with the simultaneous appearance of a firm, smooth, and moderately tender mass which becomes palpable in the region of one or both kidneys.

When renal infarction and thrombosis are suspected, Campbell has shown the importance of obtaining urographic studies as confirmatory evidence and to determine whether the condition is unilateral or bilateral. The latter information is essential to rule in or out the employment of nephrectomy.

Other conditions to be considered in the differential diagnosis are renal tumors (Wilms', neuroblastoma) with hemorrhage, hydronephrosis, polycystic kidneys, and renal carbuncle or perinephritic abscess.

Treatment.—If there is bilateral involvement, surgery is not possible, and the case will end fatally. When there is unilateral involvement, prompt nephrectomy is employed. Prior to surgery, infection, shock, dehydration, and electrolyte distortions are corrected.

At operation, the surgeon must be aware that when a thrombus is present in the renal vein and the vein is not ligated centrally to the thrombus, there is danger of its extension through the vena cava to the opposite renal vein and kidney following surgery. Accordingly, in every case, the surgeon must precisely palpate the renal vein for the presence of a thrombus prior to removal of the kidney. When a thrombus is found, the vein must be ligated on the vena cava side to prevent extension of the thrombus before removal of the kidney.

Postoperative care is directed to the provision of adequate fluids, electrolytes, protein, calories, and the prevention of infection and shock. When oliguria or anuria and azotemia persist following nephrectomy, it is probably on the basis of lower nephron nephrosis in the remaining kidney. Care must be taken to avoid overhydration in such cases.

Consideration may be given to the use of blood anticoagulants for the prevention of further thrombotic lesions following surgery. Results obtained with heparin and Dicumarol in the prevention and treatment of venous thrombosis at other sites have been encouraging. Although, to date, anticoagulant therapy has not been reported in cases of renal thrombosis, and infarction, its use would seem logical.

SUMMARY

1. A case of hemorrhagic infarction, without renal vascular thrombosis, of the right kidney in an 8-day-old male infant who survived following prompt nephrectomy is presented.

2. It is thought that this represents the fourth reported case in which the patient survived following surgery.

3. Features in the etiology, pathogenesis, diagnosis, and treatment of this disease are discussed.

4. Attention is called to the possibility of the occurrence of lower nephron nephrosis in the remaining kidney following removal of the other infarcted and/or thrombotic one.

5. A plea is made for physicians to frequently note the urinary output, to examine the urine, and to perform frequent abdominal examinations for the detection of renal masses in infants ill with infections, diarrhea, dehydration, and shock. Thus, many patients with unilateral renal infarction and thrombosis that otherwise would be overlooked will be saved by early recognition and prompt nephrectomy.

Appreciation is expressed to Colonel Jack Schwartz, M.C., Chief of Genito-Urinary Service, Letterman Army Hospital, for the accomplishment of the successful nephrectomy and his advice; and to Major Marcus Beck, M.C., pathologist, Letterman Army Hospital, for the rendition of the confirmatory pathological report.

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ENDOCARDIAL FIBROELASTOSIS

Case Reports With Special Emphasis on the Clinical Findings

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HYPERTROPHY of the heart primarily of the left ventricle associated with or due to endocardial fibroelastosis and occurring usually in small infants is a well-described entity.[1-11] In the past, most hearts with this condition have probably erroneously been labelled *congenital idiopathic hypertrophy*[2] and some *fetal endocarditis*.[3] Recently, a number of papers have appeared in the literature on endocardial fibroelastosis but most of these have been case reports with emphasis on the pathological findings. In general, most of these patients died suddenly within the first twenty-four to forty-eight hours after the apparent onset of symptoms and so there was little opportunity to make extensive clinical observations. (In this connection, it should be emphasized that this syndrome must be added to the increasing list of possible causes of "sudden death" in infants.)[12]

A recent paper by Lewis[10] has included more of the clinical signs and symptoms found in patients with endocardial fibroelastosis. She likewise has suggested that some patients might live for some time, particularly if maintained on digitalis.

The purpose of this communication is to present twenty-one cases of endocardial fibroelastosis, in some of which observations were made over a period of months and years, emphasizing the clinical aspects of the syndrome in the hope that the diagnosis of this condition can be made clinically in the future. Four of the above twenty-one patients are still alive and so the diagnosis is still a clinical one in these; the remaining have all been examined at post mortem. The problem of differentiating this condition from the usual types of congenital and acquired heart disease will likewise be discussed.

Table I summarizes the data on the twenty-one patients. Since the clinical data are so similar the case reports of only two of the patients who died and two of the living patients are presented.

CASE REPORTS

Case 1.—B. S., a female infant, was in good health until 2½ months of age at which time she developed a respiratory infection and, associated with this, dyspnea and cyanosis. Physical examination on admission to the hospital revealed the following positive findings: mild cyanosis, dyspnea, fever, râles in both lung fields, cardiomegaly but no heart murmurs, and hepatomegaly but no peripheral edema. Laboratory examination revealed a normal hemoglobin, white cell count, differential and urinalysis. The electrocardiogram revealed a normal axis deviation with diphasic T_1, T_2, and T_3 waves but no definite evidence of hypertrophy on the standard unipolar precordial leads. X-ray examination of the heart on admission revealed marked diffuse enlargement, but later this seemed to be due to right ventricular, and right and left atrial enlargement as seen in Fig. 1.

From the Department of Pediatrics University of Minnesota.

TABLE I. DATA ON TWENTY-ONE PATIENTS

PT.	SEX	AGE ONSET	DURATION ILLNESS	AGE DEATH	URI	DYSPNEA	CYANOSIS	DIFF. FEEDIN
R. T.	F	2 mo.	4 mo.	6 mo.	O	⊕	+	⊕
S. P.	F	4 mo.	--	4 mo.	O	⊕	+	⊕
J. C.	F	2 mo.	1 da.	2 mo.	O	⊕	+	⊕
B. F.	F	1 mo.	0	1 mo.	O	O	O	⊕
J. O.	M	3 mo.	1 da.	3 mo.	O	O	O	⊕
Y. C.	F	6 mo.	3 da.	6 mo.	⊕	+	—	⊕
F. T.	M	6 mo.	0	6 mo.	O	O	O	O
M. B.	M	2 mo.	4 da.	2 mo.	⊕	+	+	—
M. P.	F	4 mo.	3 da.	4 mo.	—	⊕	+	—
B. M.	M	1 mo.	14 da.	1½ mo.	—	⊕	+	⊕
M. S.	F	11 mo.	3 da.	11 mo.	—	+	+	+
G. P.	M	4 mo.	4 da.	4 mo.	O	⊕	+	—
S. S.	F	2½ mo.	14 da.	3 mo.	⊕	O	O	O
C. M.	M	2 mo.	½ da.	2 mo.	O	+	+	⊕
G. H.	F	3 mo.	3 mo.	6 mo.	O	+	O	O
B. S.	F	2½ mo.	4 mo.	6½ mo.	⊕	+	+	O
K. J.	F	3 mo.	2 yr.	2½ yr.	⊕	+	+	O
D. E.	M	7 mo.	—	Alive	⊕	O	O	O
M. B.	F	3½ mo.	—	Alive	⊕	+	+	⊕
S. S.	F	17 mo.	—	Alive	O	⊕	O	⊕
C. V.	M	8 mo.	—	Alive	⊕	+	O	+

+ Finding present.
⊕ Finding was presenting complaint.
O Finding not present.
– Finding not known as to presence.

The patient responded well to antibiotics, digitalis, and oxygen on four separate occasions and so was discharged from the hospital each time only to return several weeks later. At 6 months of age a heart catheterization was performed to determine the type of intracardiac defect. As can be seen in Table II, there was no evidence of any left-to-right shunt demonstrated and the pressures were entirely within normal limits. Following this it was postulated that the patient might have coronary insufficiency secondary to an anomalous origin of the left coronary artery from the pulmonary artery. This was based on the clinical picture plus the changes on the electrocardiogram and the absence of any intracardiac left-to-right shunt as demonstrated by the heart catheterization. Surgery was performed by Dr. Richard Varco in an attempt to increase the arterial blood flow to the muscle of the left ventricle. A systemic artery was anastomosed to the left pulmonary artery and in turn a surface of the left lung was sutured to the left ventricle. The patient died several hours after the operation.

TABLE II. RIGHT HEART CATHETERIZATION DATA ON FOUR PATIENTS WITH ENDOCARDIAL FIBROELASTOSIS

PATIENT	AGE	SEX	PRESSURE IN MM. MERCURY			OXYGEN CONTENT IN VOLUMES %					ARM-TO-LIP CIRC. TIME	ARM-TO-LUNG CIRC. TIME
			RA	RV	PA	VC	RA	RV	PA	FA		
B. S.	7 mo.	F	0/–6	16/0	16/12	9.2	9.1	8.5	9.2	--	8 sec.	4 sec.
K. J.	2 yr.	F	--	35/0	35/20	9.7	10.2	9.7	9.7	14.6	8 sec.	7 sec.?
D. E.	14 mo.	M	--	12/0	12/10	6.3	6.7	7.4	7.7	12.2	11 sec.	--
M. B.	7 mo.	F	6/2	42/5	40/16	8.6	6.7	6.9	7.1	--	--	--

Post-mortem examination revealed the heart to weigh 130 grams; the right ventricular wall was 0.3 cm. thick and the left ventricle 1.0 cm. thick. The coronary arteries were

WITH ENDOCARDIAL FIBROELASTOSIS

VOMITING	HEART MURMUR	RIGHT HEART FAILURE	SUDDEN DEATH	HEART WEIGHT (GRAMS)	NORMAL HEART WEIGHT (GRAMS)	SIDE INV.	VALVES INV.	MYOCARDIAL HYPERTROPHY
±	—	O	+	100	31	Lt.,	O	+
+	—	O	+	90	27	Lt.	O	—
—	—	O	O	50	21	Lt.	O	—
O	—	O	+	40	20	Lt.	O	—
+	O	O	+	72	23	Lt.	O	—
—	—	+	O	105	31	Lt.	O	O
O	O	O	⊕	95	31	R & L	O	—
—	+	—	O	100	23	Lt.	Mitral	—
+	—	+	O	80	27	Lt.	O	—
—	O	+	O	—	20	Lt.	Aortic	—
+	+	⊕	+	114	70	Lt.	O	—
—	+	+	O	97	27	R & L	Pulmonary	—
O	—	—	+	73	23	Lt.	O	+
O	—	+	+	65	23	Lt.	O	+
O	—	O	+	160	31	Lt.	O	+
O	O	O	O	130	33	Lt.	O	+
O	+	O	O	300	80	Lt.	Mitral	+
O	O	O	O	—	—	Lt.	—	—
O	+	O	O	—	—	Lt.	Mitral	—
O	+	+	O	—	—	Lt.	Mitral	—
+	+	+	O	—	—	Lt.	Mitral	—

normal with respect to their origin and distribution. There was a white thickening of the endocardium of the left ventricle grossly, and microscopically the endocardium was two to three times normal in thickness. There was a marked increase in fibrous tissue elements of the endocardium and some of these changes along with edema extended into the coronary arteries but without producing apparent obstruction. The muscle fibers of the myocardium were hypertrophied but there was no evidence of necrosis or inflammation within the myocardium.

The post-mortem diagnosis was endocardial fibroelastosis.

CASE 2.—K. J., a female infant, was apparently well until 3 months of age at which time she developed a respiratory infection and, associated with this, dyspnea and cyanosis. Physical examination on admission to the hospital revealed the following positive findings: mild cyanosis, dyspnea, fever, râles in both lung fields, cardiomegaly, a systolic murmur best heard in the fourth left interspace over the mitral area, and hepatomegaly but no evidence of peripheral edema. Laboratory examination revealed a normal hemoglobin, white cell count, differential, and urinalysis. The electrocardiogram revealed a Pardee Q_3, notched P_1, peaked P_2, elevated P_2, and an increase in the voltage of $QRS_{2,3}$. (An electrocardiogram taken at 2½ years of age revealed a normal axis deviation, but marked left ventricular hypertrophy and a prolonged ventricular activation time as seen in Fig. 2.) X-ray examination of the heart revealed marked diffuse enlargement with marked enlargement of the left atrium as seen in Fig. 3.

The patient responded well to oxygen, digitalis, and penicillin, and was discharged from the hospital in nine days. She was readmitted to the hospital six additional times between the ages of 3 months and 2½ years. On three occasions it was for treatment of heart failure to which she responded well each time; on two occasions, once in infancy and once at 2 years of age, she was admitted for heart catheterization. These procedures on both occasions showed no evidence of a left-to-right intracardiac shunt, and, as can be seen in Table II, the second procedure revealed a slight pulmonary

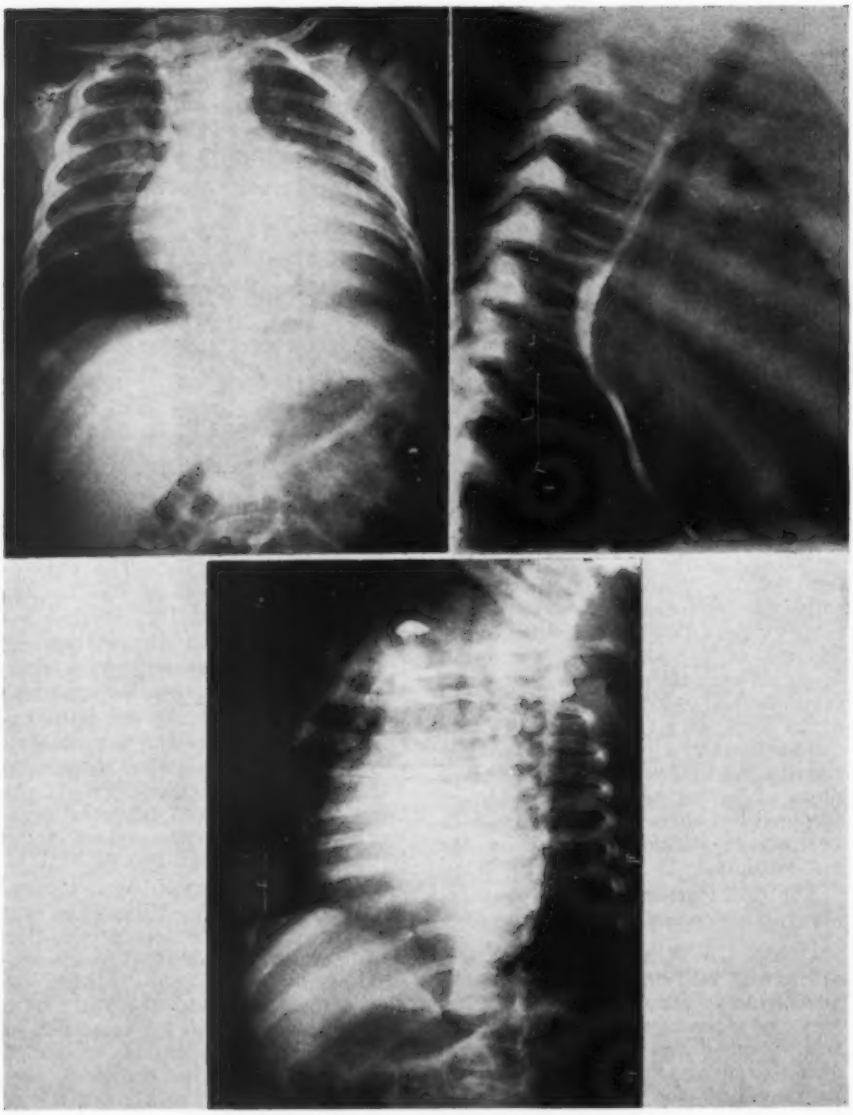

Fig. 1 (Case 1).—Roentgenograms of patient B. S., initially seen at 2½ months of age and who died at 6½ months of age. Note marked left ventricular enlargement in *a* and *c* and left atrial enlargement in *b*. Note also in *a* the normal vascular markings and pulmonary artery segment thus helping to exclude a left to right shunt.

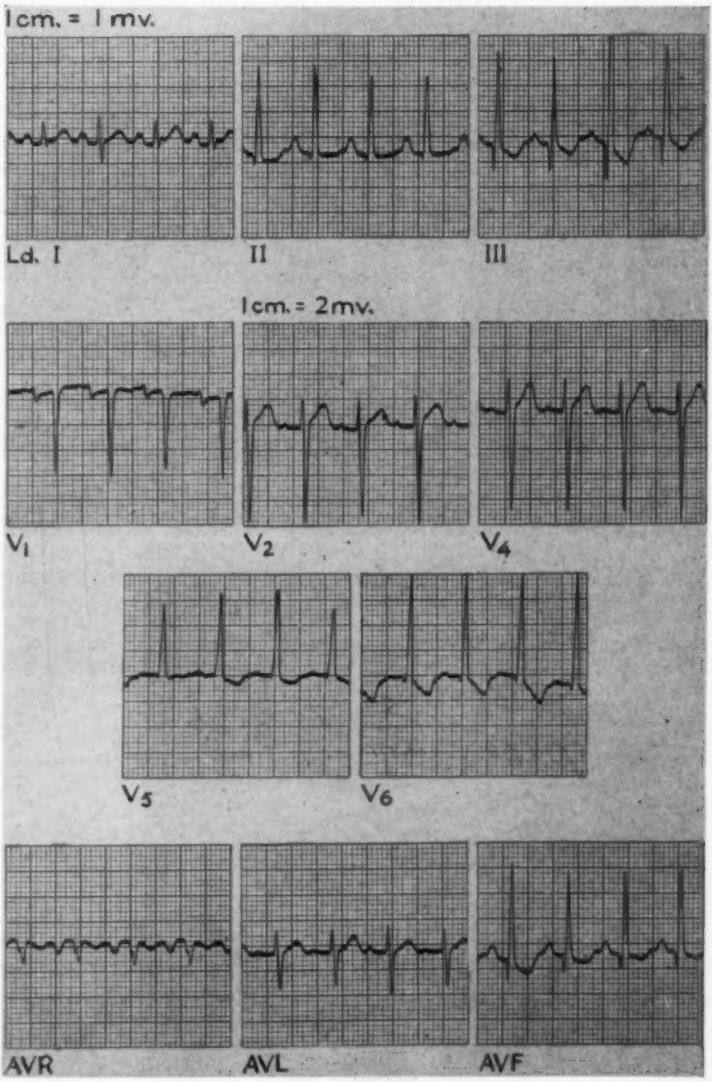

Fig. 2 (Case 2).—Electrocardiogram of patient K. J., taken at 2½ years of age. Note normal axis deviation, but evidence of marked left ventricular hypertrophy as indicated by high R wave and prolonged ventricular activation time in V_5.

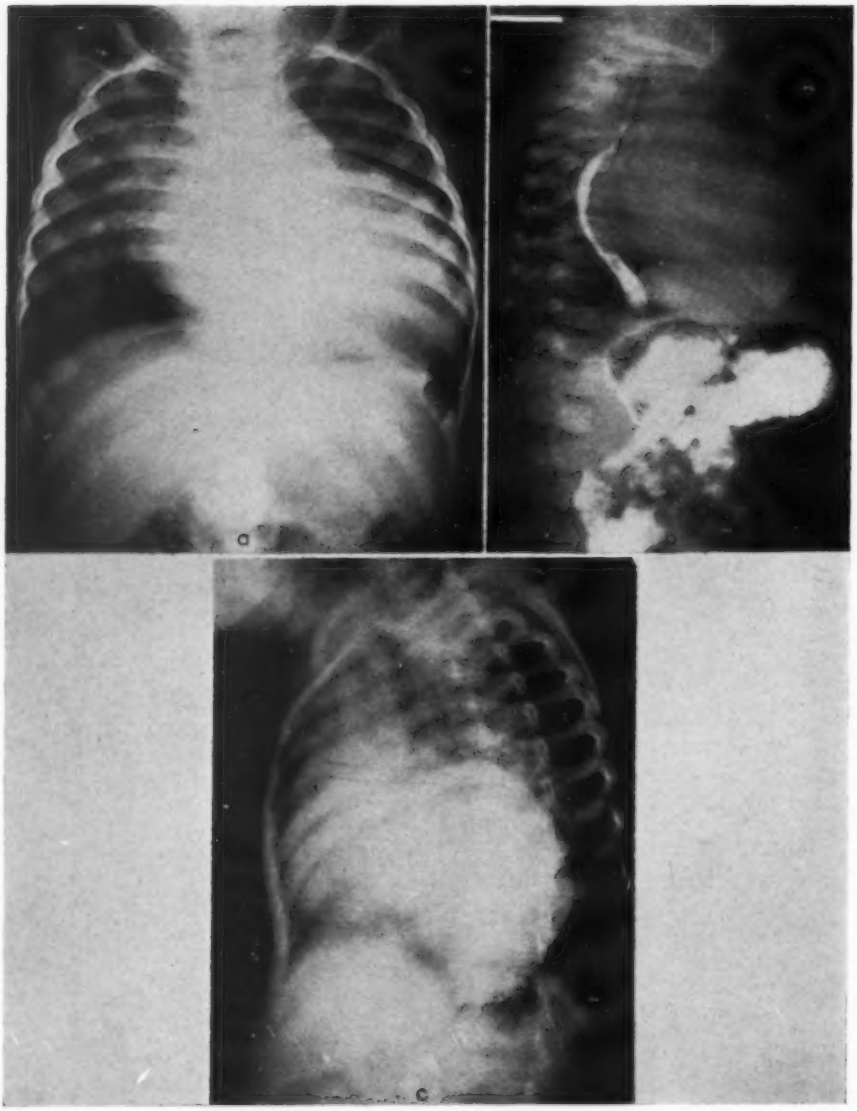

Fig. 3 (Case 2).—Roentgenograms of patient K. J., initially seen at 3 months of age and who died at 2½ years of age. Note resemblance of x-rays to patient B. S. (Fig. 1), i.e., large left ventricle and left atrium and relatively normal vascular markings and pulmonary artery segment.

hypertension of 35/20 mm. of mercury.

The patient's seventh hospital admission at 2½ years of age was for the purpose of surgically relieving the mitral lesion which it was felt was producing chronic heart failure. The patient's heart stopped beating during induction anesthesia, and by cardiac massage it was once again started. At this time careful inspection of the heart revealed that the coronary arteries were very white and that there was a large exudative lesion on the left anterior part of a dilated ventricle apparently the result of a myocardial infarction. Further surgery was not performed and the chest was closed. The child did poorly for several days finally expiring ten days after the operation.

Post-mortem examination revealed the heart to weigh 300 grams. The left ventricle was approximately six times larger than the right ventricle, and the wall was 1.5 cm. thick. The entire lining of the left ventricle was milky white in color and fibrinous to touch. This involved the mitral valve producing insufficiency and also the left atrium. There was a patch of exudate about 3 cm. in diameter over the external surface of the left ventricle; microscopically this contained fibrin and leukocytes. The coronary arteries appeared to be normal. The endocardium of the right side of the heart was normal. Microscopically on the left side of the heart there was a thick fibroelastic layer under the endocardium. This was thickest in the atrium. The myocardium was hypertrophied and there was no evidence of necrosis or inflammation within it. Elastic tissue stains revealed an overabundance of elastic tissue fibers with extension of some into the valve leaflets.

The post-mortem diagnosis was endocardial fibroelastosis.

Case 3.—D. E., a male infant, was perfectly well until 7 months of age when he developed a chronic respiratory infection with a prolonged febrile course. This was associated with diarrhea and listlessness. Physical examination revealed a chronically ill-appearing infant with fever, and cardiomegaly and extrasystoles, but with no heart murmur and no peripheral edema.

Laboratory examination revealed a white blood cell count of 28,000 with 32 per cent polymorphonuclears, 8 per cent eosinophils, and 60 per cent lymphocytes. The hemoglobin and urinalysis were normal. An electrocardiogram showed left axis deviation, depressed $ST_{1, 2}$, diphasic $T_{1, 2}$ and premature extrasystoles. X-ray examination of the heart showed 4 plus enlargement of the left ventricle, emphysema of the left lower lobe of the lung, and normal vascular markings as seen in Fig. 4.

Initially the child was seen by Dr. Erling Platou of Minneapolis who thought the infant most likely had congenital heart disease with a superimposed endocarditis. One blood culture revealed a coagulase negative *Staphylococcus albus* which was resistant to penicillin and streptomycin. The infant was put on aureomycin and was given two blood transfusions; following this the fever disappeared and the general condition improved. He was discharged after three weeks of hospitalization. Four months later he was readmitted to the hospital with a three-week history of fever, mucoid loose watery stools, pallor, and listlessness. At this time the white blood cell count ranged from 9,000 to 14,000 with a normal differential. The sedimentation rate, hemoglobin, and urinalysis were all normal.

The boy was transferred to the University Hospitals at 14 months of age for a definite diagnosis of his heart lesion. As seen in Table I, heart catheterization revealed no evidence of a left-to-right shunt or abnormality of pressures. It was felt he had primarily left heart disease such as is found in endocardial fibroelastosis. He was discharged from the hospital on prophylactic sulfadiazine and when last seen at 2½ years of age he was doing well according to the mother.

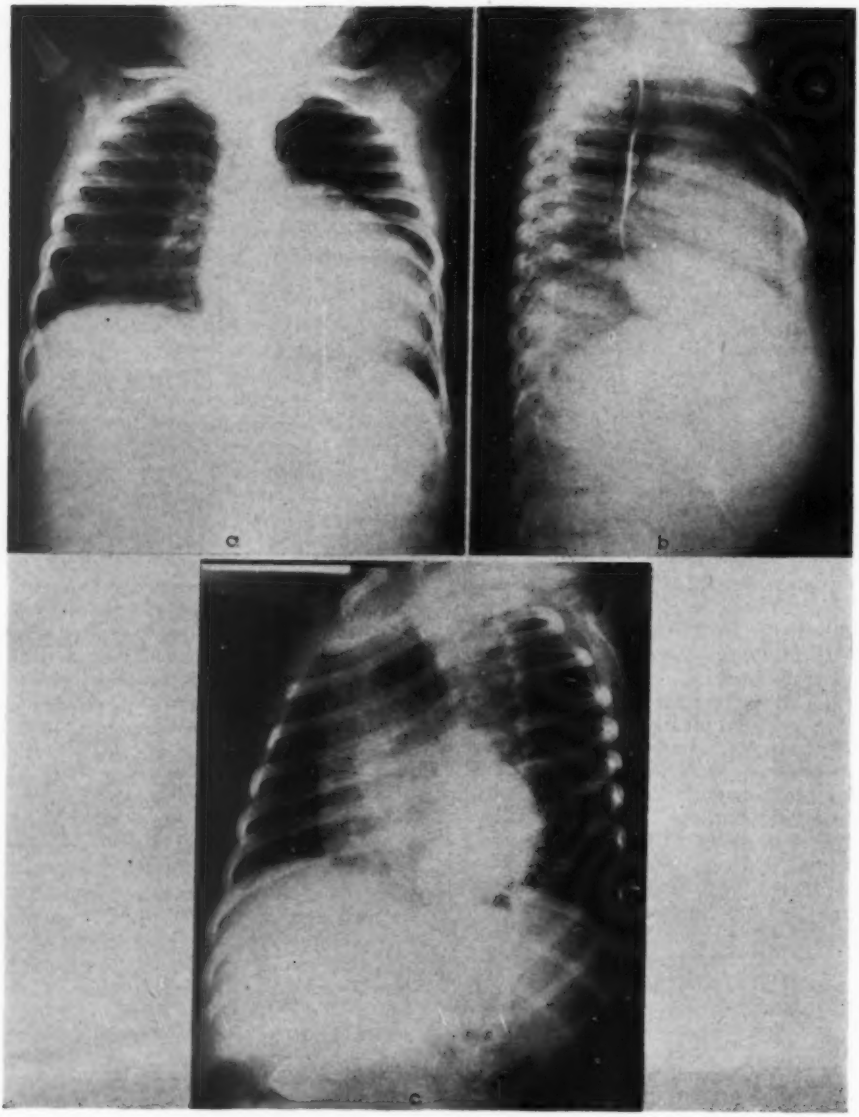

Fig. 4 (Case 3).—Roentgenograms of patient D. E., initially seen at 7 months of age and who is still alive at 2½ year of age. Note enlarged left ventricle in *a* and *c*.

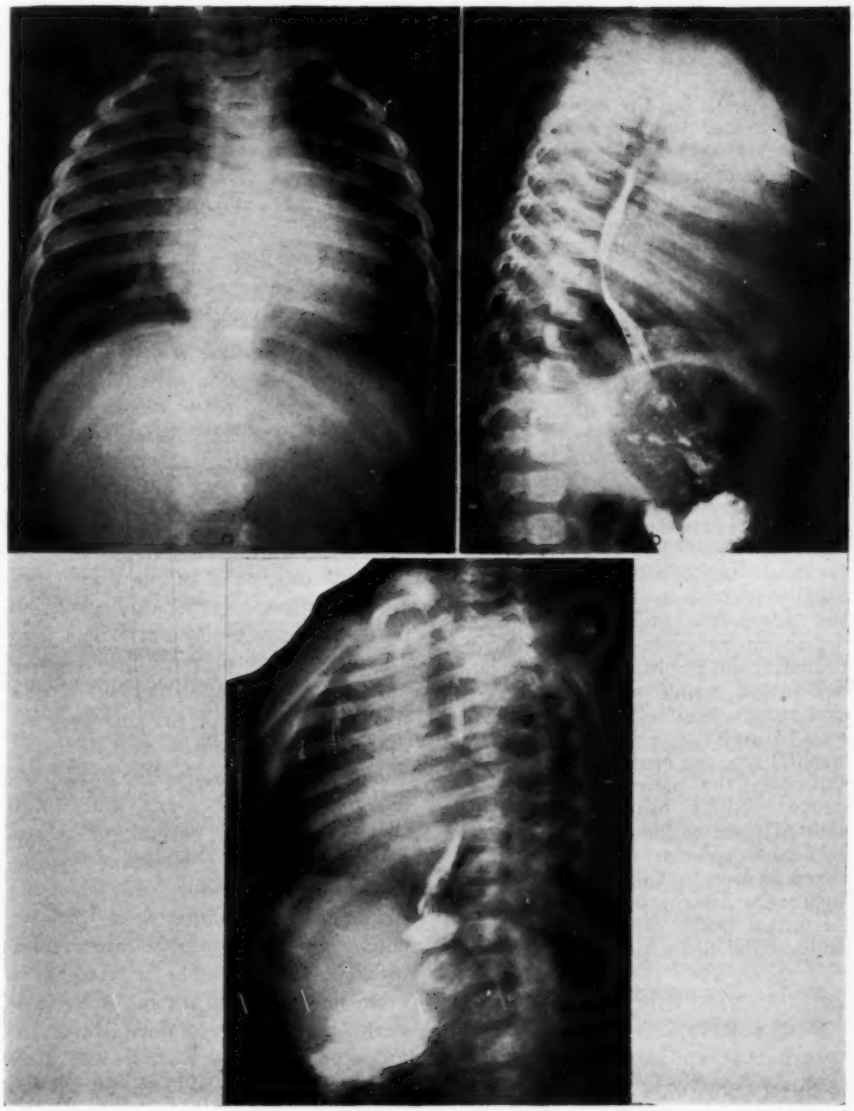

Fig. 5 (Case 4).—Roentgenograms of patient M. B., seen initially at 3½ months of age and who is still alive at 7 months of age. Note enlarged left ventricle in *a* and *c* and left atrium in *b*.

Examination revealed a small but healthy-appearing child with an enlarged heart and extrasystoles. The electrocardiogram still showed a left axis deviation but the T waves and S-T segments had become normal.

CASE 4.—M. B., a female infant, had had anorexia, poor weight gain, and frequent respiratory infections since birth. A heart murmur with associated cardiac enlargement was first noted at 3½ months of age. The infant was first hospitalized at 5 months of age because of an otitis media. During this hospitalization, x-ray examination revealed an enlarged left atrium and probable enlargement of the left ventricle as seen in Fig. 5. An electrocardiogram revealed peaked P_1 and P_2 waves with depressed S-T segments.

The infant was readmitted to the hospital again at 7½ months of age because of increasing dyspnea, and associated cyanosis. The weight gain had been poor. Physical examination revealed malnutrition, tachycardia, cardiomegaly, a systolic murmur over the mitral area, and no fever.

Laboratory examination revealed a normal hemoglobin, white cell count, differential, urinalysis, and sedimentation rate. The "C" reactive protein was 14 and the mucoprotein tyrosine was 3.9 mg. per cent. Following digitalization the patient seemed to improve. Right heart catheterization showed some pulmonary hypertension but no evidence of a left-to-right shunt as seen in Table II. These findings were interpreted as possibly due to mitral heart disease secondary to endocardial fibroelastosis.

DISCUSSION

Our observations confirm those of others that endocardial fibroelastosis occurs primarily in infancy and early childhood. Clinically the symptomatology may be of very short duration before death occurs or no symptoms may be present at all thus producing apparent "sudden death." On the other hand, symptoms may be present for many months and even years before causing death and it would appear likely that some patients regain enough cardiac reserve to go on and live a fairly normal life even though the heart remains enlarged.[10] Such patients need to be followed over a longer period of time before one can properly state the natural history of the disease.

Symptoms.—It would appear from our cases and those of others that the major symptoms in endocardial fibroelastosis are related to left heart failure possibly precipitated and accompanied by respiratory disease. These would be dyspnea, cyanosis, listlessness, and vomiting.

Physical Findings.—Physical examination usually reveals an acutely or chronically ill infant with fever, dyspnea, cyanosis, râles in the lungs, cardiomegaly, possibly hepatomegaly, but usually no peripheral edema. A mitral or aortic murmur may or may not be heard, depending upon how severely the valves are involved by the sclerotic process.

Laboratory Examination.—The hemoglobin, white count, and differential are usually normal unless secondary bacterial infection accompanies the respiratory disease. The urinalysis, tuberculin test, Wassermann, and sedimentation rate are also usually normal. The electrocardiogram may reveal a normal or left axis deviation on the standard leads, but unipolar precordial leads usually show evidence of marked left ventricular hypertrophy. In addition there are changes compatible with anoxemia and strain of the heart, e.g., low, negative, or diphasic T waves; depressed S-T segments; and normal or in-

creased amplitude of the QRS voltage. Evidences of myocarditis are usually absent such as conduction prolongation, etc. The typical electrocardiographic changes are illustrated in Fig. 3.

Roentgen examination usually reveals a markedly enlarged heart primarily of the left side with little or no evidence of a left-to-right shunt such as an increase in the pulmonary vascular markings and a prominent pulmonary artery segment.

Course of the Disease.—As mentioned earlier, some patients die so early that the diagnosis cannot be suspected clinically. Other patients tend to have recurrent episodes of left heart failure usually precipitated by respiratory disease. In contrast to patients with congenital heart disease, patients with endocardial fibroelastosis seem to respond better and more quickly to digitalis and oxygen. Since most of our patients also have had respiratory disease, we have given one or more of the antibiotics. In between episodes of left heart failure, we have attempted to keep these patients on prophylactic chemotherapy or antibiotics to prevent respiratory disease, and digitalis has been continued in some instances.

Differential Diagnosis.—In those patients with heart murmurs, the differential diagnosis usually is between one of the more common congenital heart conditions and endocardial fibroelastosis. Any congenital heart lesion with a left-to-right shunt can usually be eliminated by: the absence of such evidence on the x-ray examination (increased pulmonary vascular markings and pulmonary artery segment); the absence of right ventricular hypertrophy on the electrocardiogram; and negative evidence by right heart catheterization as seen in Table I.

As stated by Taussig[13] and Gibson[14] the diagnosis of an anomalous origin of the left coronary artery can be made by the characteristic electrocardiographic findings of inversion of the T waves in all three leads *combined with curves of low voltage.* It should be noted that one of Lewis'[10] patients and also one of our patients were erroneously suspected of having an anomalous origin of the left coronary artery and in both surgery was attempted to increase the flow of oxygenated blood to the left ventricle.

The usual patient with a congenital mitral or aortic lesion can usually be differentiated from endocardial fibroelastosis by the relative benignancy of the congenital valvular lesion early in infancy and the absence of anoxemia changes on the electrocardiogram.

In those patients *without* a heart murmur the differential diagnosis is usually between myocarditis and endocardial fibroelastosis. Myocarditis usually produces diffuse cardiac enlargement rather than left-sided enlargement and electrocardiographically the changes are more likely to be prolongation of conduction, and lower voltage of the various complexes. Usually in myocarditis, particularly of the rheumatic type, one finds elevation of the "acute phase" reactants[15] whereas in endocardial fibroelastosis it has been our experience that these have been normal or only slightly elevated.

It would thus appear that endocardial fibroelastosis can be diagnosed clinically in certain instances. We feel that the etiology remains obscure, however. Recently Hill and Reilly[11] have suggested that endocardial fibro-

elastosis might be one of the collagen diseases and they presented evidence based on tissue staining to support this thesis. It is difficult for us to accept this hypothesis because:

1. Fibroelastosis only rarely involves the myocardium.

2. Usually there is no microscopic evidence of inflammation within the myocardium.

3. Acute phase proteins usually do not become elevated.

4. Elastic fibers are occasionally present in the heart valves of patients with endocardial fibroelastosis and these have not been observed in the collagen diseases.

SUMMARY

1. The case histories of four infants and children who were thought to have endocardial fibroelastosis have been presented. In the two patients who died, the typical gross and microscopic changes of endocardial fibroelastosis were found.

2. The typical signs, symptoms, physical findings, and laboratory findings have been described for this disease.

3. The course of the disease was shown to be fulminating in some infants, whereas in others there were periodic episodes of left heart failure eventually leading to death. It was postulated that some patients survive the initial disease and go on to live a relatively normal life in spite of cardiomegaly.

4. The differential diagnosis has been discussed. It was concluded that endocardial fibroelastosis can be diagnosed clinically.

5. Evidence has been presented to negate claims that endocardial fibroelastosis is one of the collagen diseases.

The authors are indebted to Dr. James Dawson, Professor of Pathology, and Dr. Benjamin Clawson, Professor Emeritus of Pathology, for their help with the pathological material.

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A STUDY OF THE HYPNOTIC EFFECT OF DORMISON IN CHILDREN

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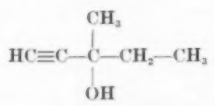
IN VIEW of the importance of rest in the treatment of tuberculosis, Dormison* was assayed on a group of children with tuberculosis.

This is a report of a clinical study of the effects of Dormison over a period of four months on 1- to 12-year-old tuberculous patients of the Pediatric Division, Sea View Hospital. The Pediatric Division is housed in one large modern building consisting of nine wards, containing twenty-five beds each. The children are segregated according to sex, age, degree of tubercular involvement, and presence of intercurrent infections. The children's hospital daily routine includes morning and afternoon rest periods which are observed by all children except those who are attending instructions. Evening retirement depending upon age occurs between 6 and 7:30 P.M.

CHEMISTRY AND PHARMACOLOGY OF DORMISON

Dormison is an unsaturated aliphatic carbinol called 3-methyl-pentyne-ol-3.[1] Its structural formula is:



The LD_{50} of Dormison in several species of animals ranged between 600 and 900 mg. per kilogram which is approximately seventy times the adult human dose.[2] Caffeine parenterally rapidly counteracted deep hypnosis in animals induced by large overdoses of Dormison. Metabolic studies[3] have indicated the rapid metabolism of the drug which probably explains the low incidence of side actions reported in clinical studies.[4]

SELECTION OF PATIENTS

It was determined that there were approximately thirty children who, because of varying degrees of restlessness, might be considered subjects to whom Dormison would be beneficial. The categories of this group were as follows:

I. Gross mental deficiencies—Mongolian idiots, residuals of meningitis, etc. Some were on regimens of barbiturates.

II. "Nervous" children.

a. Those who never rest during the morning and afternoon rest periods.

b. Those exhibiting long presleep periods of restlessness and agitation.

III. A third group of twenty-five children having normal mentalities was also used to test the hypnotic and sedative properties of Dormison.

Some of the measurable behavior patterns among these children which might be influenced by a hypnotic or sedative drug were:

A. Hyperactivity during rest periods.

B. Prolonged wakefulness before going to sleep at night.

C. Enuresis and those who are awakened during sleep for toilet training.

D. Late afternoon fatigue.

E. Children previously requiring sedation with other drugs.

From the Division of Pediatrics, Sea View Hospital for Tuberculosis, Department of Hospitals.

*This drug in the form of a palatable elixir was generously supplied to us by Dr. Norman L. Heminway and Dr. Abbott W. Allen of Schering Corporation, Bloomfield, N. J.

COLLECTION AND ANALYSIS OF DATA

The following data were gathered from residents' and nurses' observations and notes taken during this study. Instead of observing one (or both) of the rest periods, some of our patients started schooling. This increased activity often made them quieter during the remaining rest period and at bedtime. When this was noted, Dormison was discontinued in such children who manifested fatigue, in order to avoid false conclusions on the effects of this drug. Initially, Dormison was administered in doses of 50 mg. to children in all groups regardless of age. This dose was used as a base line and was found to be inadequate except in rare instances. The dose was then raised to 100 mg. and in some cases to 300 mg. With more adequate dosage, the following observations were made.

Larger doses had to be given for the rest periods than for bedtime and the over-all results were not as gratifying. However, we were studying essentially the hypnotic and sedative effect rather than anesthetic action. We found that in using 100 to 300 mg. we were able to keep the majority of the children quiet who formerly were agitated and restless. In a small percentage (less than 20 per cent) of the cases, at the dosage employed we obtained total sleep during the prescribed rest hours. Dormison worked satisfactorily as a sedative in the mental deficiency group. In the majority of this group, although sleep was not obtained, we were able to keep the children quiet, whereas previously they were usually a disturbing influence to others in the ward. A prolonged period of wakefulness before retirement at night was a factor in 81 per cent of our children. The presleep time, or the time required to go to sleep, ranged on an average from 15 minutes to 3½ hours. With Dormison, the average presleep period dropped to a range of 5 to 30 minutes and the concomitant restlessness was definitely curtailed. The usual effective bedtime dose was 100 to 250 mg. Dormison was more efficacious as a prebedtime medication than in other applications.

The sleep of these children appeared more sound. However, when awakened they did not appear more groggy than usual or manifest other signs of residual somnolence. In fact, they appeared more refreshed and active than they did prior to Dormison.

The majority of the patients in the mental deficiency group on the whole responded favorably to Dormison. These children were receiving phenobarbital to control their activities prior to this study. The barbiturates were discontinued during the test period.

In the gross mental deficiency group there were eight cases. In the "nervous" (hyperactive) group there were twenty-four cases. In this total of thirty-two cases the following observations were made: nine patients established a behavior pattern at bedtime after withdrawal of Dormison. None established a behavior pattern during the day after the withdrawal. There were twelve patients where Dormison was more successful at bedtime than during the day. There were twenty-four patients who reverted to their former habits either during the day or at bedtime (or both) after withdrawal of Dormison. Ten patients showed little or no effect with Dormison during the daily rest periods.

Dormison given at bedtime to the group with normal mentalities made them more active than usual the following day. This was interpreted as being due to a more rested condition rather than any latent stimulating effects of the drug.

DOSE IN RELATION TO AGE

We could find no relationship between dosage and age. The usual approach was 100 mg. (4 c.c.), and then after observing the results, to increase the dose, if necessary up to 300 mg. daily. We believe the average dose to be 150 mg., some requiring more and some requiring only 100 mg. In cases tested with 500 mg. (20 c.c.), we found that approximately 75 per cent became more active. Since Dormison was used in the form of an elixir containing about 4 per cent ethanol, we assumed that the alcohol may have acted as a stimulant, probably related to cortical release as a result of its depressor effect.

EFFECTS OF WITHDRAWAL AND RESUMPTION OF DRUG

In nine of the thirty cases, when Dormison was stopped after one month of continual use, the pattern established under Dormison therapy remained for varying lengths of time up to three months. This phenomenon was much more evident at bedtime and in relatively recent hospital arrivals. This study is being continued.

In the mental deficiency group, Dormison withdrawal resulted in a reversion to their former hyperactive habits and the patients had to be returned to Dormison promptly. Five of the thirty cases, who received beneficial effects with 50 mg. at the beginning of the study, began to show evidence of ineffectiveness of the drug. When the dosage was increased to 100 mg. or more, the beneficial effects returned and have persisted to date. Further study on possible developed tolerance should be done.

NEUROLOGICAL OBSERVATIONS

In order to assess any neurological changes that might have resulted from the use of Dormison, we took at random twenty-five children who fell into various age groups, ten from the 1- to 2-year age group; ten from 4 to 6 years of age; five from the 7- to 10-year-old group.

These children were given between 150 and 200 mg. for a period of ten days. They were observed upon awakening and also 1½ hours later. The 1- to 2-year age group, because of lack of cooperation, could be studied only by gross methods of observation. The older age groups were tested for straight line walking, light response, Romberg, nystagmus and pass pointing.

In no instance was any deviation from the normal neurological pattern observed. It was a striking observation that in no instance was a hangover noted. No patients complained of headache, dizziness, or any sense of undue somnolence.

CLINICAL LABORATORY DATA

Complete blood counts and urinalysis were done on each case prior to and after the beginning of the use of Dormison. Up to the present, there have been no changes in any instance that could be attributed to the toxicity of the drug.

WEIGHT STUDIES

Weights taken on twenty-nine children (the remaining three were bed-

ridden) who were receiving Dormison were compared with a group of comparative size and stage of tuberculosis. The average weight gain over a four-month period in the Dormison group was 2.1 pounds as compared with 1.0 pound for the control group. It is presumed, therefore, that the children relieved of their tension and wakefulness may have experienced a beneficial effect on weight gain.

PLACEBO STUDIES

The placebo vehicle used was identical in taste and odor to Dormison. The results were as follows: The placebo study was done about 2½ months after the first withdrawal study was made. There were now four patients who were no longer on Dormison because they had established a satisfactory pattern after one month on the drug. Of the twenty-eight remaining cases, six showed no change of habit with the placebo. Perhaps several of these may fall into the group tentatively labeled as those with an habituation phenomenon. However, most of these are cases which reacted poorly or not at all to Dormison. The remaining twenty-two reverted to their former habit patterns when placed on the placebo. Only one of the children in this group displayed a knowledge of the substitution, and he was one of the children who had shown only a poor to fair response to the drug originally.

REPRESENTATIVE CASE HISTORIES

CASE 10.—L. R., a 4-year-old Negro female. Diagnosis: arrested primary pulmonary tuberculosis and mental retardation. Habits: extreme agitation and restlessness, purposeless screaming at any time or catatonic-like state abnormal for a child.

The patient had previously been on barbiturates continuously. The initial dose of 50 mg. Dormison t.i.d. was not beneficial. However, at 200 mg. before morning and afternoon rest periods and 150 mg. at bedtime, the patient slept well at night and remained quiet during the day. Withdrawal of Dormison caused reversion to former habits. Reinstitution of Dormison returned patient to sleep at night and quiet during the day.

CASE 19.—A. N., a 4-year-old Puerto Rican female. Diagnosis: primary pulmonary tuberculosis and arrested tuberculous meningitis. Habits: constantly restless, does not sleep during rest periods.

After the initial dose of 50 mg. Dormison t.i.d. the patient showed an improvement during rest periods which gradually waned by the end of one week. The dosage was increased to 100 mg. t.i.d. and the patient's rest period habits improved although she did not sleep. Upon withdrawal of Dormison, the patient reverted to her former habits. When the patient was returned to Dormison, she was put on 150 mg. before rest periods and now the child sleeps during one rest period and rests quietly during the other. Since the patient now sleeps well at night, no Dormison is currently given at bedtime.

CASE 12.—A. O., a 13-year-old white female. Diagnosis: primary pulmonary tuberculosis; Mongolian idiot. Habits: restless all day; presleep restless period from 30 to 90 minutes.

Dormison 50 mg. t.i.d. was given with some beneficial effect at bedtime and there was a reduction of presleep restlessness to from 10 to 20 minutes. During the day, the patient was easier to manage. The drug was increased to 100 mg. t.i.d. and then the patient was completely quiet during her rest periods. Withdrawal effect was observed to be a reversion to her original pattern. A return to the drug again showed quiet rest periods and moderate rapid presleep induction.

CASE 26.—E. V., a Puerto Rican male, aged 4 years. Diagnosis: primary pulmonary tuberculosis; Pott's disease. Habits: restless during rest periods, long (50 to 60 minutes) presleep induction period.

Dormison was begun with a dose of 50 mg. t.i.d. There was some initial improvement but the patient returned to his former habits within two weeks. There appeared to be a tolerance developing. The dosage was then increased to 100 mg. t.i.d., but this only gave moderate improvement in restlessness. Withdrawal gave reversal to original pattern. The patient then started to attend school. Dormison was now used only at bedtime (200 mg.) which has shortened the original 50- to 60-minute presleep period appreciably.

CASE 3.—W. E., an 8-year-old Negro male. Diagnosis: progressive primary tuberculosis with cavitation—patient on pneumothorax. Habits: frequent long active preseleep period. The patient was put on 150 mg. Dormison before morning and afternoon rest periods and 250 mg. at bedtime. The nurses remarked that it was the first time they ever saw this patient asleep during a rest period.

CASE 32.—L. R., a 4-year-old Puerto Rican female. Diagnosis: primary pulmonary tuberculosis with effusion. Habits: restlessness during periods set aside for that purpose and prolonged presleep period at bedtime. After an initial dose of 50 mg. t.i.d. the patient showed some improvement and the dose was raised to 100 mg. t.i.d. This patient had enuresis and was awakened several times during the night. She did not appear more stuporous or groggy than the average child so awakened. When Dormison was withdrawn, she reverted to her former habits and so the drug was reinstituted. The dosage was increased to 200 mg. before rest periods and 100 mg. at bedtime. She now sleeps during one rest period and is quiet during the other. It is interesting to note that about two months ago (the halfway point in this study) the patient stopped her bedwetting.

It was noted in almost every instance that the patients on Dormison appeared to sleep more soundly at night.

SUMMARY AND CONCLUSIONS

1. Dormison, a new hypnotic and sedative drug, appears to be devoid of toxicity in children in doses of 50 to 500 mg. used over a period of several months.

2. The optimal hypnotic dose appears to be between 150 and 200 mg. Higher doses, such as 500 mg., appear to induce increased activity rather than sleep.

3. Comparative studies with a placebo of identical taste and appearance proved that Dormison has true hypnotic activity.

4. Although sleep was not achieved in all cases, the majority reacted favorably in this respect under the conditions discussed.

5. Induction of sleep at bedtime usually occurs between 5 and 30 minutes after the drug is taken. Dormison is a more effective hypnotic at bedtime than during the day. Sedative effects, however, could be demonstrated during the day.

6. A sleep pattern was established in certain patients after the use of this drug for a period of one month.

7. There was a signal absence of mental sluggishness, torpor, or neurological disturbances after its use.

8. Dormison-treated patients showed an average weight gain of 2.1 pounds over a four-month period, as compared with a 1.0 pound gain over the same period for the control group. This effect in the treated patients is attributed to relief from tension and

wakefulness, as well as the sounder sleep which is induced by Dormison.

9. Dormison appears to be a valuable mild hypnotic and sedative and is a useful addition to the list of hypnotics, particularly in children, because of its absence of aftereffects.

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IMPETIGO AND ACUTE INFECTIOUS EXFOLIATIVE DERMATITIS OF THE NEWBORN INFANT (RITTER'S DISEASE)

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THE presence of impetigo neonatorum in a nursery for newborn infants is universally recognized as requiring prompt institution of rigid isolation measures. The disease is not usually serious, and with proper steps taken for isolation, treatment, and prophylaxis of contacts, no great concern is caused by the appearance of sporadic cases.

Occasionally, however, impetigo may be a highly dangerous infection. Its relation to sepsis of the newborn infant is well recognized. Less well recognized, but amply clear from many reports in the literature, is its relation to exfoliative dermatitis of the newborn infant (Ritter's disease).

Most reports concerned with Ritter's disease have dealt with single cases. We could find no report of the disease in epidemic form in the United States although we know of two outbreaks other than the one reported here.

The present report deals with a biphasic nursery epidemic in which the manifestations of infection ranged from uncomplicated impetigo neonatorum to a fulminating type of exfoliative dermatitis.

PHYSICAL ARRANGEMENT OF THE DEPARTMENT AND DESCRIPTION OF THE EPIDEMIC

The maternity department involved is part of a large general hospital but occupies an entirely separate building.

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The formula kitchen is in the basement, operates with terminal sterilization, and handles nothing but formula preparation. Routine fortnightly cultures of formulas were sterile prior to and during the outbreak. Repeated cultures of formulas, nipples, bottles, water, nipple caps, and lactose solution were all sterile.

On the first floor are the business offices, outpatient clinics, residents' quarters, waiting rooms, and several unused private rooms.

The ward nursery is located on the second floor and houses eighteen bassinets and two incubators. The private nursery is on the third floor and houses fourteen bassinets.

Nursery techniques for the nurses included the wearing of gowns and caps but no gloves or masks. Nurses scrubbed to the elbow upon coming on duty and washed hands between babies.

Physicians wore gown and cap and used brush and hand scrub on entering the nursery, followed by an alcohol sponge. At times nurses were assigned to both floor and nursery on the same period of duty. There was crossing between nurseries on the part of both physicians and nurses.

No culturing or physical examination of personnel was carried out.

Prior to the epidemic there had been no skin infections or other cause for isolation among the infants for several months.

There were no isolation facilities functioning on an organized basis. Up to the time of this outbreak, suspect isolation had been accomplished by utilizing a vacant patient room as necessary.

Before describing the exact chronology of the outbreak it will simplify later discussion to delineate the four types of cases that were encountered. A single description of each type may serve for all infants in each group.

Group A. Pustular Pyodermia of the Scalp.—A single case characterized by a few small, rather firm, yellow pustules of the scalp. These lesions were relatively deep-seated and could not be rubbed off readily. This was the first skin infection of any sort in many months.

Group B. Bullous Impetigo Neonatorum.—These cases presented typical impetigo of the newborn infant. The babies had one to many thin blister-like lesions of very superficial nature. These lesions varied from pinhead- to dime-size and were filled with a clear to cloudy fluid, depending on the age of the lesion. These blebs rubbed off very easily, leaving a smooth reddened base. There was seldom any marked degree of inflammatory reaction around these lesions. The institution of over-all twice-a-day examination revealed that an infant could be completely free of lesions at one examination and show several well-developed lesions a few hours later. Some, but not all such infants, showed positive Nikolsky's sign after initial blebs appeared.

Group C. Infants Showing Positive Nikolsky's Sign But No Blebs or Pustules.—Nikolsky's sign was sometimes encountered in infants showing no other skin lesions or signs of illness at the time the sign was discovered. Every such infant received vigorous therapy once the importance of the sign was realized. Even with vigorous therapy such infants always showed exfoliation over limited areas within forty-eight hours of detection of positive Nikolsky's sign.

Group D. Acute Fulminating Systemic Illness With Exfoliation of the Skin (Ritter's Disease).—Some infants in this group had one or more vesicular skin lesions (impetigo) before the onset of acute illness while others never had a detectable skin lesion prior to the beginning of massive exfoliation. With or without initial skin lesions the clinical picture was most characteristic once it was recognized as an entity.

Refusal of feedings was invariably the earliest sign of illness. In the absence of any abnormal physical findings, an infant would suddenly refuse most or all of a scheduled feeding. This was followed by regurgitation and vomiting of progressive severity and frequency.

Prostration, lethargy, and marked abdominal distention followed with alarming rapidity. Mucoid green stools appeared on the second day and a shocklike state supervened.

Some of the infants became rapidly jaundiced and others did not.

Fever was usually absent but in two instances reached 102° F. Leukocytosis was present in two cases but absent in others.

Desquamation usually began on the second or third day and left a red, moist, raw-looking area. During the last few hours of life the superficial layers of skin often hung in large shreds after exfoliation from sizeable areas. In the fatal cases large areas of epidermis could be sloughed off with gentle pressure at autopsy.

The entire acute illness in three instances was of less than thirty-six hours' duration from the first refusal of food to death.

When the nature of the problem was recognized and intensive treatment instituted, the pattern of the disease was altered and in some instances recovery ensued after a stormy course.

In the later phases of this experience some infants were given intensive treatment almost on suspicion and could only be classified finally as Rit-

ter's disease when during treatment, and just prior to recovery, more or less extensive exfoliation occurred.

It has been repeatedly stated in the literature that exfoliation usually begins on the face. In our cases there was no single site of predilection. It was noted as beginning on the folds of the neck, groins, scrotum, axillary region, or on the face.

tained. The baby recovered at home where its physician used Furacin ointment locally.

Within twenty-four hours it was reported that an infant sent home from the *second* floor nursery had developed "blisters" at home. No culture was obtained.* This patient was treated

TABLE I.

CASE NO.	DATE	TYPE CASE	SITE OF CULTURE	ORGANISMS	SENSITIVITIES	COAGULASE ACTIVITY
1	8/24/48	Impetigo	None			
2	8/24/48	Impetigo	None			
3	8/28/48	Impetigo	None			
4	8/29/48	Impetigo	Skin. v. fl.	St. aur. hem.	Pen-R. Strep-S.	--
			Stool	E. coli		
5	8/29/48	Impetigo	Skin. v. fl.	St. aur. hem.	Pen-R. Strep-S.	--
			Blood	St. albus		
				E. coli		
6	8/29/48	Ritter's disease	Skin	St. aur. hem.	Pen-R. Strep-S.	--
			Pharynx	St. aur. hem.	Pen-R. Strep-S.	--
			Blood	No growth		
7*	8/30/48	Ritter's disease	Skin. s. ep.	St. albus		
8*	8/31/48	Ritter's disease	Skin. s. ep.	St. aur. hem.	Pen-R. Strep-S.	--
			Rectal	E. coli		
9	8/31/48	Ritter's disease	Skin. s. ep.	St. aur. hem.	Pen-R. Strep-S.	--
			Pharynx	St. albus		
			Stool	E. coli		
10	8/31/48	Ritter's disease	--	--	--	
11	9/ 3/48	Impetigo	Skin. v. fl.	St. aur. hem.	Pen-R. Strep-S.	Pos.
12	9/ 4/48	Impetigo	None			
13	9/ 4/48	Impetigo	None			
14	9/ 5/48	Impetigo	None			
15	9/ 6/48	Impetigo	Skin. v. fl.	St. aur. hem.	Pen-R. Strep-S.	Pos.
16	9/ 7/48	Impetigo	None			

Abbreviations: Skin. v. fl., Fluid aspirated from vesicles.
Skin. s. ep., Culture under freshly exfoliated skin.
St. aur. hem., Staphylococcus aureus hemolyticus.
Pos., Positive.

*Post-mortem cultures.

Chronologic Development of First Phase of the Outbreak.—The initial instance of infection was a single pustular pyodermia of the scalp on Aug. 24, 1948, in the third floor nursery (Case 1). This infant was isolated overnight in a glassed-in cubicle within the nursery and was discharged to its home the following day. While still in the hospital penicillin ointment was applied to the scalp locally and 50,000 units procaine penicillin were given intramuscularly. No culture was obtained.

with a sulfonamide ointment and promptly cleared.

On August 28, four days after Case 1, a typical case of impetigo neonatorum appeared in the third floor nursery (Case 3). This infant had several small vesicles all of which had been broken before cultures were obtained. The nursery was closed to further admissions and a report sent to the Department of Public Health. Treatment

*See Table I for summarization of cultures from patients.

was penicillin ointment locally and 50,000 units procaine penicillin intramuscularly. Within twenty-four hours all lesions were healing and no new lesions appeared. On this same day all infants in this nursery were started on 50,000 units procaine penicillin daily.

It should be remarked at this point that due to serious shortages of nursing personnel there was a certain amount of crossing back and forth by nurses between second and third floor nurseries. Usual gowning and hand washing techniques were employed.

On August 29, two more cases of impetigo occurred in the *second floor nursery* (Cases 4 and 5). Cultures were obtained and these infants were transferred to the pediatric department (separate building). The nursery was closed to admissions and all infants were started on 50,000 units procaine penicillin as in the third floor nursery.

The cultures were reported as hemolytic *Staphylococcus aureus,* coagulase positive. A later report showed them to be highly resistant to penicillin but sensitive to streptomycin.

Also on August 29, a baby in the third floor nursery developed lesions *while getting penicillin* (Case 6) but it was another forty-eight hours before the cultural evidence explained this fact.

At this point the Department of Health, to which the closure of the nurseries had been reported, gave permission for the establishment of a "clean" nursery on the first floor for the admission of new infants. An entirely separate personnel was secured and maintained for this nursery.

First Case of Systemic Illness.—Thirty-six hours after skin lesions were noted in Case 6 the baby began to refuse feedings. During the night of August 31 he began to regurgitate, and on September 1, developed sudden severe abdominal distention. A tentative diagnosis of intestinal obstruction was made and the infant was transferred to another hospital for treatment. There, under the supervision of one of us (H. F. L.), the picture described under Group D rapidly developed. The diagnosis was believed to be sepsis of the newborn infant secondary to impetigo, and intensive therapy with intravenous sulfonamides, fluids, plasma, blood, and streptomycin was begun. Forty-eight hours after becoming ill the infant showed large areas of desquamation behind the ears, in the folds of the neck and groins, and over the shoulders. Skin cultures revealed a pure culture of *Staph. aureus* matching the cultural characteristics of Cases 4 and 5 although obtained by a separate laboratory. Blood culture was sterile but was obtained after streptomycin therapy had been started. The organism from the skin was streptomycin-sensitive, penicillin-resistant.

During the same period of time that the above was going on, a 4-day-old infant (Case 7) born to a mother with late syphilis was signed out against advice because of objections to the quarantine regulations. At the time it left the hospital the infant had no skin lesions. It was returned to the pediatric service late in the same day because of vomiting, rapidly increasing jaundice, and abdominal distention. The picture was that described under Group D and again intestinal obstruction was temporarily entertained as a diagnosis by a group of physicians as yet unaware of the over-all problem. This infant survived only 18 hours

after admission and developed extensive exfoliation of the skin just prior to death on Sept. 1, 1948. No cultures were obtained prior to death. On the basis of gross findings and the maternal history of syphilis, the pathologist made a tentative diagnosis of congenital syphilis. This was undoubtedly the first recognizable case of Ritter's disease but remained undiagnosed until the hindsight of another day's experience with Case 6 as described above relegated the confusing element of probable syphilis to the background.

Case 8, third floor nursery, first showed anorexia on Aug. 31, 1948, and died Sept. 1, 1948, after transfer to the pediatric service with the Group D clinical picture (Ritter's disease).

By the time the facts in Cases 6 and 7 and the culture reports were brought together, the true significance of and relation between Cases 6, 7, and 8 became apparent. The reader should bear in mind that Cases 6 and 7 were under treatment in two separate places, that Case 7 had been removed against advice and did not again come under observation until in extremis, and that all this occurred in approximately thirty-six hours.

Post-mortem cultures from Case 8 revealed a hemolytic *Staph. aureus*, penicillin-resistant, streptomycin-sensitive.

The cultures from Cases 4, 5, 6, and 8 gave support to the regime of therapy under which Case 6 was by this time recovering. Penicillin prophylaxis and therapy were stopped on all infants on the third day after the first case of systemic illness occurred.

Another infant (Case 9) in the second floor nursery became anorexic on Aug. 31, 1948. By September 2, this baby presented signs seen in Group D, was transferred to the treatment unit in the pediatric department, and recovered after intensive treatment and moderate exfoliation.

Case 10 left the hospital on August 31, 1948, in apparently good health, but was readmitted thirty-six hours later to a nearby hospital in poor condition and died presenting the full-blown Group D picture.

It will be noted that Cases 6, 7, 8, and 9 all became ill within one twenty-four-hour period August 31, and that the onset in Case 10 occurred at home on the following day. The appearance of serious illness with such rapidity made an over-all evaluation very difficult indeed. However, it was the data gathered on these initial cases which made possible prompt and successful therapy in some of the later cases.

On September 3, four days after the first evidence of any serious illness was recognized, the hospital closed the entire maternity department. By the evening of this day the situation was clarified as data and cultural information from the various infants were correlated. The Department of Public Health, having been informed of the entire problem, permitted the establishment of a completely isolated unit in the pediatric department of the hospital for the treatment of any further cases that might develop and for the continued treatment of those infants already ill. This involved complete living-in within the unit for members of the resident and nursing staff assigned to this duty and presented many difficult problems.

After the first three days there was good integration of the staffs of the maternity and pediatric departments

and of the resident, laboratory, and nursing staffs.

Unstinting cooperation was received from the Philadelphia Department of Public Health which assigned a physician to full-time work on the problem and began the systematic field follow-up of all infants discharged on and after Aug. 24, 1948. From Sept. 3 to 16, 1948, five previously discharged infants were found to have impetigo at home. Two, Cases 11 and 15, were returned to the treatment unit for therapy. Both showed pure cultures of Staph. aureus hemolyticus in blister fluid. Both recovered. Three minimal cases were treated at home and recovered (Cases 12, 13, 16).

After penicillin was discontinued, each infant in the nurseries was given a daily over-all inunction with approximately 4 Gm. of Furacin ointment (Furacin soluble dressing).

There were no further cases of Group D type in this primary outbreak and only one other case of impetigo (Case 14).* No case of any sort developed in the first floor "clean" nursery which had admitted seven infants prior to the complete closing of the department. Total nursery population during the above period was fifty-three infants.

In third floor nursery there were four cases of uncomplicated impetigo and two cases of Ritter's disease. One infant recovered and one died.

In second floor nursery there were seven cases of uncomplicated impetigo, and three cases of Ritter's disease. One infant recovered and two died.

*This case developed in spite of the prophylactic application of Furacin. A change was made to a single over-all application of 5 per cent sulfathiazole in water-soluble base on the day of delivery according to the technique of Weymuller, and Ittner.[12]

With the closing of the maternity department, arrangements were made for delivery of registered patients at other hospitals.

Nasopharyngeal cultures were taken from the entire personnel including all physicians who had had any contact with the nurseries or delivery rooms. Formulas, water, oils, lotions, alcohol, caps, masks, cribs, mattresses, the penicillin, stretchers, resuscitators, linens, thermometers, all solutions, brushes, tap water, powder, bottles, nipples, and incubators were cultured in a search for an environmental source of the organism. None was found.

Hemolytic *Staph. aureus* was obtained from some of the personnel but no culture was penicillin-resistant and streptomycin-sensitive as were all of the cultures so tested from the involved infants.

From Sept. 3, 1948, until the last infant was discharged all infants in the nurseries were inspected twice daily by the staff and immediately prior to discharge by the Department of Public Health physician assigned to the epidemic. The infants were then followed every forty-eight hours at home by the Department of Public Health until it was certain that no further trouble would develop.

After the last infant was discharged the building was entirely renovated. Everything paintable was painted. Where painting or autoclaving was not feasible surfaces were sprayed with Roccal solution.*

Prior to this epidemic the techniques and methods in use were considered adequate. They were at least as good as those in use in the better-class institutions in the community with certain exceptions, such as a lack of

*Solution benzalkonium chloride.

proper isolation facilities and interchange of nursing personnel from one nursery to the other and from floor duty to nursery duty.

Revisions of management instituted after this outbreak included the establishment, on a permanent basis, of a properly equipped and staffed isolation nursery, the assignment of nurses to nursery duty only and to only a single nursery, more rigid scrub technique and emphasis on careful handwashing between babies, installation of elbow-control faucets throughout, ultraviolet screens at nursery doors, and limitation of visitors to mothers.

Secondary Phase of the Epidemic.—The maternity department had been reopened on Sept. 16, 1948,* and, except for one questionable case of impetigo with a single lesion, there were no cases of infection until Dec. 5, 1948, when a case of typical impetigo neonatorum with many small superficial blebs developed in the *second* floor nursery (Case 17). This infant was 7 days old and showed no other signs of illness. A culture of fluid aspirated from the lesions yielded hemolytic *Staph. aureus,* coagulase positive and sensitive to penicillin, streptomycin, and sulfonamide. The infant was given 100,000 units procaine penicillin and discharged the same day. Further penicillin at home resulted in prompt recovery.

Four days later on December 9, in the same nursery, a 3-pound 4-ounce male premature infant began to refuse feedings. He then developed vomiting, jaundice, lethargy, and abdominal distention. (Case 18.) There were no skin lesions. He was transferred to the pediatric service where he died within twelve hours of the first signs of illness. The terminal picture was that of the Group D infants in the prior outbreak (Ritter's disease).*

On the same day another infant developed a similar picture. There were no skin lesions. This infant also was a premature male weighing 5 pounds 2 ounces. He was transferred promptly but despite intensive treatment cyanosis and labored respiration rapidly developed. Extensive desquamation appeared and the baby died less than twenty-four hours after illness was first suspected.

Both the above infants received intravenous fluid, plasma, oxygen, penicillin, streptomycin, and sulfadiazine. Both were typical of the Group D clinical picture.†

The second floor nursery was closed immediately upon discovery of the illness in Case 19 and prior to the definite diagnosis. Cultures of equipment, personnel, and formulas were begun at once.

Prophylactic inunction with sulfathiazole ointment was begun again for all infants on the day of birth and a single inunction for all infants already in the nursery.

On the evening of the same day premature twins in the same nursery developed anorexia and regurgitation but no other signs of illness (Cases 20 and 21). On this slight evidence both were transferred to the pediatric service and treatment started at once. One infant developed abdominal distention, diarrhea, and desquamation of the skin of the chin and scrotum but he went on to gradual recovery. The other twin developed typical desquamation of the

*Prophylactic inunction with sulfathiazole ointment was not reinstituted at this time.

*See Table II for summary of cultural studies on patients in this second phase of the epidemic.

†See summary of post-mortem findings for discussion of autopsy findings.

scrotum and thighs but this healed rapidly and he also recovered.

Late at night of the same date, December 9, in the same nursery, an 11-day-old full-term white male refused his feeding and vomited once. There were no other findings (Case 22). He was transferred at once and treatment was started. The following day there was abdominal distention, vomiting, and desquamation of the thighs, scrotum, and a lesser amount on the neck. This infant went on to recovery, and treatment was discontinued after six days.

More detailed studies at the onset in Cases 21 and 22 would have been of great interest but one cannot temporize with an illness in the newborn infant which progresses from apparent health to death in thirty-six hours!

All these infants were from the second floor nursery. During this second phase of the epidemic there was no crossing of personnel between nurseries and the infection remained confined to the one nursery.

Following the above cases there were no further instances of impetigo or illness. In this second outbreak the

TABLE II.

CASE NO.	DATE	TYPE CASE	SITE OF CULTURE	ORGANISMS	SENSITIVITIES	COAGULASE ACTIVITY
17	12/5/48	Impetigo	Skin. v. fl.	St. aur. hem.	Pen-S. Strep-S.	Pos.
18*	12/9/48	Ritter's disease	Skin. s. ep.	St. aur. hem.	Pen-S. Strep-S.	Neg.
			Blood	E. coli		
			Bowel	E. coli		
			Lung	St. aur. hem.	Pen-S. Strep-S.	Neg.
19*	12/9/48	Ritter's disease	Skin. s. ep.	St. aur. hem.	Pen-S. Strep-S.	Pos.
			Blood	E. coli		
			Pharynx	St. aur. hem.	Pen-S. Strep-S.	Neg.
			Rectal	E. coli		
20	12/9/48	Ritter's disease	Skin. s. ep.	St. aur. hem.	Pen-S. Strep-S.	Pos.
			Pharynx	E. coli		
			Urine	St. aur. hem.	Pen-S. Strep-S.	--
21	12/9/48	Ritter's disease	Skin. s. ep.	St. aur. hem.	Pen-S. Strep-S.	--
			Blood	No growth		
			Pharynx	St. aur. hem.	Pen-S. Strep-S.	--
			Rectal	E. coli		
22	12/9/48	Ritter's disease	Pharynx	St. aur. hem.	Pen-S. Strep-S.	--
			Rectal	E. coli		

*Immediate post-mortem cultures.

We feel that these last three cases were all definite instances of the same disease which had proved so highly fatal. In these last cases treatment was begun almost on suspicion but subsequent developments supported the wisdom of this course. Both the cultures (see Table II) and the subsequent signs supported the diagnosis.

While treatment was prompt in Cases 19 and 20 there was the added factor of prematurity in these infants and they did not survive.

Department of Public Health again followed up every infant in the field who had been discharged for five days prior to the first case and followed all infants sent home later. No additional cases were discovered.

As a result of the detailed investigations of a special committee a number of regulations were formulated and put into effect. It was realized that most, if not all, of the factors covered quite probably had no bearing on what had occurred. The aim, how-

ever, under the urgent pressure of the circumstances, was to set up as flawless a technique as possible.*

As a result of the cultural studies the committee felt that a nasopharyngeal reservoir was the most likely source of the offending organism. The entire staff, including physicians, maids, and janitors, was subjected to complete physical examination in a search for sources of the staphylococcus believed to be responsible. Nose cultures and throat cultures were done twice on every individual. All those positive for hemolytic *Staph. aureus* whether coagulase positive or negative were excluded and given a course of 300,000 units procaine penicillin for five days. After an interval of at least forty-eight hours following treatment they were recultured. In most instances the hemolytic staphylococci had disappeared. Readmission to the service was not permitted until a negative culture was obtained for hemolytic *Staph. aureus*. As expected, about one-third of the individuals had positive cultures at the outset. When such a culture involved a nursery nurse she not only underwent the above regime but also was excluded from the maternity service for at least three weeks.

SUMMARY OF POST-MORTEM FINDINGS ON FOUR INFANTS WITH EXFOLIATIVE DERMATITIS

An analysis of the findings in the four infants on whom post-mortem studies were done revealed, with certain variations, comparable pathology in each.

Lung: All lungs but one showed moderate to extreme capillary engorgement with alveolar hemorrhages. All showed some degree of focal or diffuse atelectasis. In only two was an alveolar exudate present and in these a sparse exudate of polymorphonuclears indicated a terminal pneumonia.

The pulmonary findings were suggestive of shock and a terminal atelectasis presumably due to weakened respiratory effort.

Liver: All showed cloudy swelling and edema with exudate of polymorphonuclears, eosinophils, and macrophages in periportal connective tissue. Fatty degeneration was present in two cases.

Small intestine: Polymorphonuclear exudate in the mucosa of the small intestine of all patients was the most consistent sign of inflammation in any internal organs of the group.

Adrenal: There was engorgement of medullary capillaries. The cells of the zona reticularis were partly foamy and largely eosinophilic. Cells of other zones had abundant pink homogeneous cytoplasm. The foamy cells in the zona reticularis were absent in one infant.

Kidney: There was swelling of the convoluted tubules and edema of pelvic submucosa in all cases.

Skin: The skin lesions were studied in three patients. They were essentially similar, consisting in a coagulation necrosis of the cells of the malpighian layer and a separation of the epidermal layers at this point. This was accompanied by some edema of the epidermis and by the formation of vesicles or blebs which ruptured. All four, in addition, showed localized foci of necrosis and exfoliation of the entire epidermis and coagulation necrosis of the underlying corium. These lesions resembled second and third degree burns. In only one of the three was a polymorphonuclear exudate present. The positive skin cultures indicate the presence of staphylococci at this site, and the absence of local leukocytic response in the skin may merely reflect the lack of resistance displayed by many infants to staphylococcus toxin. In two infants cocci

*The regulations as finally adopted met and sometimes went beyond every requirement or suggestion set forth in the *Standards and Recommendations for Hospital Care of Newborn Infants* published by the American Academy of Pediatrics, with the single exception of square footage of space per infant.

also were demonstrated on the skin surface by tissue stains, and in the third infant smears of the deep layers of the skin showed cocci.

DISCUSSION

The epidemiology of impetigo neonatorum has been the subject of much study. It has been clearly shown that a nasopharyngeal reservoir on the part of personnel plays a large part in the spread of the infection.[13, 14]

While it has sometimes been maintained that impetigo neonatorum and dermatitis exfoliativa neonatorum are not pathogenetically similar, the evidence indicates that certain strains of staphylococci are capable of producing either or both clinical pictures. Severity of infection no doubt depends upon the usual variables bearing upon infections plus the very important factor of degree of maturity of the individual infant. In our experience the course of the infection was extremely rapid and the prognosis particularly bad in premature infants.

Epidemic occurrences of dermatitis exfoliativa neonatorum have been unusual. When they have been observed it has been in association with cases of ordinary appearing impetigo.

Our own experience re-emphasizes the dangerous potential of any pustular or bullous lesions occurring in nurseries. In the absence of precise knowledge of the pathogenic potential of an infecting organism, every skin infection in nursery practice must be considered dangerous not only for the infant involved but particularly for its contacts.

In the outbreak of infection herein described there was impetigo of varying superficial appearance ranging from small, firm pustules confined to the scalp to large, thin-walled, bullous lesions. At the same time other infants, sometimes without visible impetiginous skin lesions, showed varying evidence of systemic illness and exfoliative dermatitis (Ritter's disease). The severity of the latter condition ranged from slightly positive Nikolsky's sign to extensive exfoliation and death.

There was much evidence to indicate that a hemolytic *Staph. aureus* was the causative organism. We concur in the opinion that Ritter's disease is fundamentally an acute bacterial infection of the neonatal period. In no single instance was a hemolytic streptococcus isolated in our studies despite the fact that a large number of cultures were made. This adds further weight to the validity of the staphylococcic etiology.*

Although the staphylococcus believed to have been the etiological agent was invariably recovered from the skin lesions and often from several other sites at post mortem, it was not recovered in blood cultures in those instances where these were made. This is in accord with previous experience. Only rarely have positive blood cultures been reported. Whether there is a transient stage of bacteremia remains unproved.

The tissue findings were compatible with the portal of entry being either the skin or the gastrointestinal tract. The histology plus the rapid and violent systemic reaction suggested the presence of a potent (presumably staphylococcic) toxin.

Control of this outbreak was not satisfactory until emphasis was put upon rigid cultural control of nursery personnel with exclusion of all those

*Studies of the coagulase activity of the isolates seemed inconclusive. Subcultures varied in both directions from the isolate.

with nasopharyngeal cultures positive for hemolytic staphylococci plus the prophylactic inunction of all exposed infants with 5 per cent sulfathiazole in a water-soluble ointment base.* No infant receiving this prophylactic inunction developed any sign of infection.

The use of sulfathiazole in this manner has been questioned in terms of the possibility of the development of sulfonamide sensitization. We have found no evidence in the literature or in our own experience that such an application *in the newborn period* produces sensitization. On the contrary, there is good evidence that sensitization is *not* produced.[17, 18, 19] The procedure has been shown to be highly effective in the prevention of the occurrence of epidemic impetigo in nurseries when a single case has occurred.[17, 18]

The topical use of injectable antibiotics tends to produce resistant strains of bacteria and should be avoided in nursery practice. Admittedly with the multiplication of wide-spectrum antibiotics this factor is of less importance than previously.†

SUMMARY

A biphasic nursery outbreak of impetigo neonatorum and dermatitis exfoliativa neonatorum (Ritter's disease) is described. There were twelve cases of uncomplicated impetigo and ten cases of Ritter's disease.

Of the ten infants with Ritter's disease, five died and five recovered. Only when therapy could be started with the earliest signs of illness was a fatal outcome prevented.

The evidence suggests that a *Staph. aureus* hemolyticus was the causative organism. The epidemic was not finally controlled until all personnel with nasopharyngeal cultures positive for hemolytic *Staph. aureus* were rigidly excluded from the nurseries.

The authors wish to express their gratitude to Dr. William P. Warga who did most of the bacteriologic work here reported.

The sick infants were treated, with few exceptions, in the Children's Hospital of the Mary Drexel Home (associated with Lankenau Hospital). The management of these cases was carried out by the medical, resident, and nursing staffs of that institution in a special unit set up for the purpose, under the direction of Dr. Emily Bacon and Dr. Edward H. Vick.

We wish to express our thanks also to the Philadelphia Department of Public Health and, in particular, to Dr. Angelo Perri, Director, Division of Communicable Diseases, and to Dr. Sylvan M. Fish who carried out the field work.

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*Sulfathiazole is no longer council-accepted. Bacitracin or Neomycin ointments should prove equally effective.[20]

†At the time this epidemic occurred, aureomycin, terramycin and Chloromycetin were not yet in general clinical use.

MOLYBDENIZED FERROUS SULFATE (MOL-IRON) IN THE TREATMENT OF THE ANEMIA OF PREMATURE INFANTS

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INTRODUCTION

IN VIEW of reports which indicate that molybdenized iron is well tolerated and that molybdenum potentiates the utilization of absorbed iron in various forms of iron deficiency anemia,[1, 2, 3] we have been led to investigate the influence of this compound on the development of the anemia of premature infants.

The anemia which develops uniformly in the premature infant has been attributed at least in part to inadequate stores of iron and poor hematopoesis at a time of rapid growth and expansion of the vascular bed and may be divided into two different types, the early type being physiologic and the late type pathologic.[4, 5] Differentiation of these types is based on the duration and severity of the anemic state. Some investigators have advocated delaying iron therapy until the pathologic anemia has developed on the thesis that the bone marrow will not respond to iron therapy during the period of physiologic anemia,[4] while others[5] have presented evidence that the early administration of iron is more effective in ameliorating the anemia than therapy which is delayed until the late or pathologic type has developed.

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METHODS

Premature infants weighing between 1 and 2 kilograms at birth were divided into the following three groups: (1) Fifteen infants received 20 mg. of iron daily as molybdenized iron (1 c.c. Mol-Iron Liquid twice daily); (2) fifteen infants received 20 mg. of iron daily as solution of iron and ammonium citrates (1 c.c. of a 5.9 per cent solution twice daily); (3) ten infants received no iron therapy and served as controls. All infants included in this study received 0.6 c.c. of an aqueous polyvitamin preparation daily beginning on the fifth day of life and all were given powdered milk formula to tolerance. Iron therapy was begun on the fifth day of life in Groups 1 and 2. Data were compiled on all three groups simultaneously in order to obviate the possibility that slight variations in nursery care might exert an influence on the results.

The following variables were measured on the first and fifth day of life and thereafter at ten-day intervals until the infants attained a body weight of 2.5 kilograms:

1. Hemoglobin by the photoelectric determination of oxyhemoglobin.[6] This was standardized by the oxygen content method of Van Slyke.[7]

2. Hematocrit by the capillary tube method as described previously.[8]

3. Erythrocyte count using a Spencer hemocytometer.

4. Reticulocyte count by the wet brilliant cresyl-blue staining method.

5. Mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume were calculated[9] from the above measured data.

6. Weight was determined daily.

RESULTS AND DISCUSSION

The results of this study are presented graphically in Figs. 1, 2, 3, and 4. In each figure the symbols denote the mean values and the vertical lines denote plus or minus one standard deviation from the mean. Statistical analysis involved the determination of the critical ratio.* Since the groups receiving iron therapy demonstrated a similar hematologic response, they were combined and compared with the control group on the twenty-fifth and fifty-fifth days of life.

The hemoglobin concentration (Fig. 1) was similar in all groups on the first day of life and remained so during the first twenty-five days of life. After twenty-five days, it is apparent that the group receiving molybdenized iron tended to develop a less severe anemia than the group receiving iron in the form of iron and ammonium citrates although the latter group shows some advantage over the group receiving no iron therapy. A statistical comparison between the treated and untreated groups revealed no significant difference at the time the infants were 25 days of age. At age 55 days, however, the critical ratio was 2.46 which is a significant difference at the 5 per cent level.

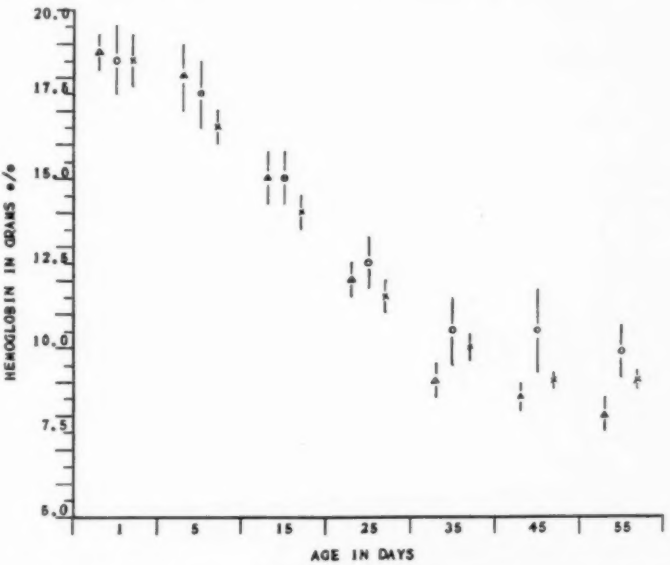

Fig. 1.—Graphic representation of mean (± one standard deviation) of hemoglobin concentration. Δ=control group; O=Mol-Iron group; X=iron and ammonium citrate group.

*Critical ratio = mean difference ÷ standard error of the difference.
Standard error of the difference =

$$\sqrt{\frac{(N_1 + N_2) \cdot (\Sigma d_1^2 + \Sigma d_2^2)}{N_1 \cdot N_2 \left[(N_1 - 1) + (N_2 - 1)\right]}}$$

in which N_1 = number in control group, N_2 = number in iron-treated group, Σd_1^2 = sum of squared deviations in the control group and Σd_2^2 = sum of squared deviations in the iron-treated group.

The hematocrit (Fig. 2) followed a pattern similar to that of the hemoglobin. Statistical analysis revealed no significant difference between control and treated groups on the twenty-fifth day. On the fifty-fifth day the critical ratio was 2.61 which again is significant at the 5 per cent level.

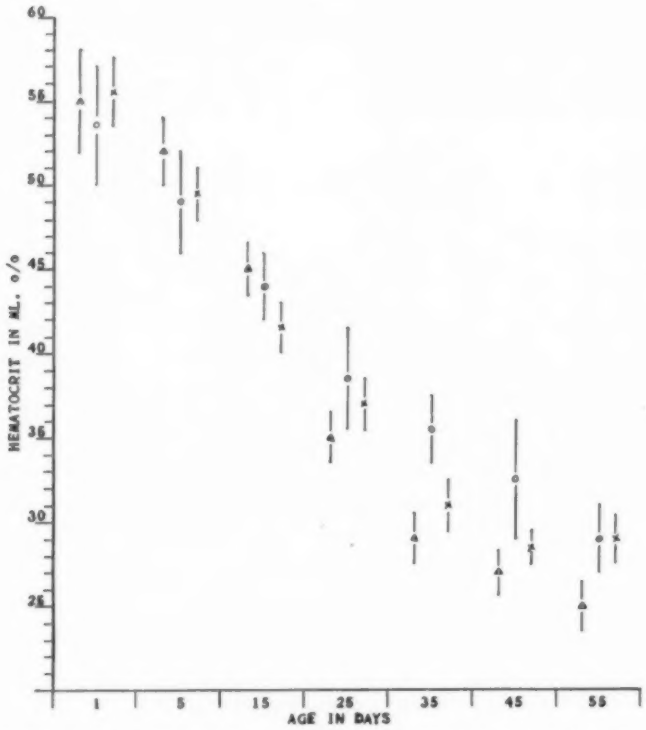

Fig. 2.—Graphic representation of mean (± one standard deviation) of hematocrit. Δ=control group; O=Mol-Iron group; X=iron and ammonium citrate group.

Fig. 3 demonstrates that progressive changes occur in the erythrocyte count in each of the three groups which are practically identical with changes in the hematocrit. There was no significant difference in erythrocyte count between treated and untreated groups on either the twenty-fifth or fifty-fifth day of life, however. This may well have been influenced by the rather wide range of values encountered in this determination.

Reference to Fig. 4 reveals that some advantage might be attributed to iron therapy insofar as reticulocyte response of these premature infants is concerned, there being a slight but consistent advantage of molybdenized iron. Again, comparing treated with untreated groups, there was a significant difference at age 55 days at the 5 per cent level (critical ratio 2.51) and no significant difference at age 25 days. Our inability to exert any control over

these patients after they were discharged from the nursery prevented follow-up studies. We are therefore unable to state the eventual effect of iron therapy on the course of the anemia in these infants.

treated group, 1,614 grams. The control group gained an average of 19.9 grams daily and the iron-treated group 20.3 grams daily. This observation tends to obviate the possibility that a difference in rapidity of expan-

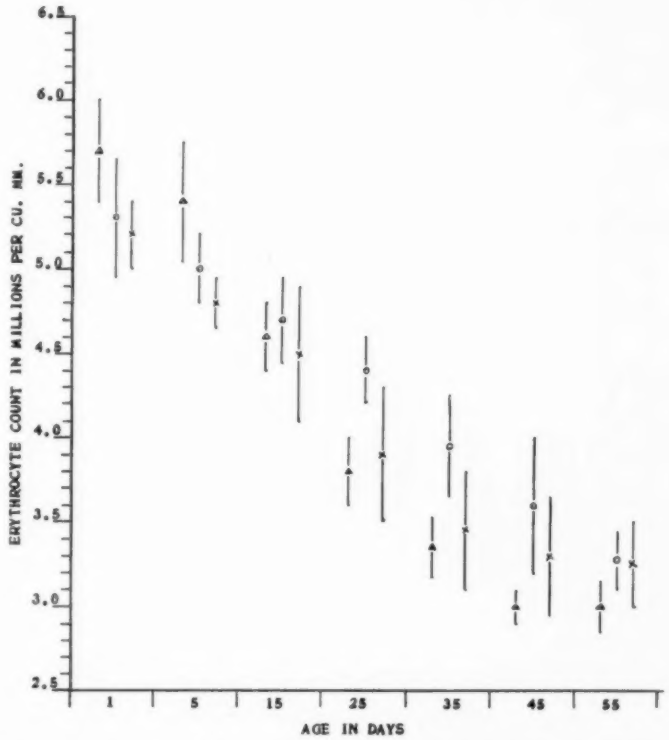

Fig. 3.—Graphic representation of mean (± one standard deviation) of erythrocyte count. Δ=control group; O=Mol-Iron group; X=iron and ammonium citrate group.

Because of the nature of the trends of the measured variables listed above there were no significant differences between the three groups in the calculated values (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration).

The birth weight of the control group was 1,587 grams, of the iron-

sion of the blood volume in the two groups might have influenced the hematologic results.

During these studies we observed no intolerance to molybdenized iron in the form of Mol-Iron Liquid and in no case was it necessary to discontinue the drug. On the other hand, three infants receiving iron and ammonium citrates had to be dropped

from the study because they developed rather severe gastroenteritis which cleared promptly when the preparation was discontinued.

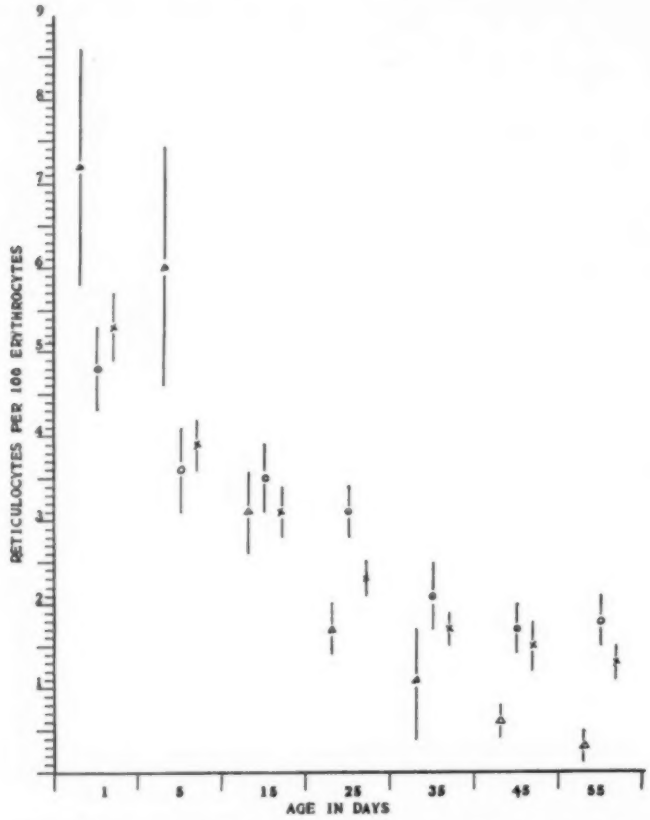

Fig. 4.—Graphic representation of mean (± one standard deviation) of reticulocyte count. △=control group; O=Mol-Iron group; X=iron and ammonium citrate group.

These results indicate that the administration of iron during the period of prematurity is beneficial insofar as the anemia is concerned and that there is some advantage to be gained by using molybdenized iron.

SUMMARY AND CONCLUSIONS

1. The effect of molybdenized iron (Mol-Iron Liquid) and solution of iron and ammonium citrates on the hemoglobin, hematocrit, erythrocyte count, reticulocyte count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and daily weight gain have been determined in thirty premature infants weighing between 1 and 2 kilograms at birth. Ten premature infants receiving no iron therapy served as controls.

2. Those infants receiving iron therapy tended to develop a less severe

anemia than the control group and in this respect there was some advantage of molybdenized iron over iron and ammonium citrates.

3. Molybdenized iron (Mol-Iron Liquid) was well tolerated by these premature infants.

Hematologic determinations were made by J. M. Montalvo, B.S.

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POLYMYXIN B IN PSEUDOMONAS AND PROTEUS ENTERITIS

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Pseudomonas aeruginosa and proteus species, though normally present on the skin and in the intestinal tract of man, occasionally demonstrate unquestionable pathogenicity in the production of fatal septicemia as well as local suppuration in otitis, meningitis, pyelonephritis, endocarditis, arthritis, pneumonia, superficial wounds, and burns.[1, 2, 3, 4, 5] Their role in the production of enteritis, particularly infantile diarrhea, remains in doubt. However, the necrosis of the intestinal wall with perforation and death in debilitated infants due to *Ps. aeruginosa* which was reported by Schaffer and Oppenheimer[6] demonstrates without doubt an at least occasional causative role. Most studies of the relationship of these organisms to infantile diarrhea[1, 6, 7, 8, 9] have only demonstrated their simultaneous presence with diarrhea, the absence of other known pathogenic agents, or the statistically greater frequency of their occurrence in patients with diarrhea. The clinical picture of enteritis presumably due to these organisms has not been sufficiently distinct to permit an evaluation of their constant presence or their isolation. Though they are pathogenic and can be reisolated in animals, no proof of their relationship to human enteritis is thereby obtained. This evaluation is further confused by the observation that invasion by these organisms will only occur under certain conditions in the host: (a) debilitation,[5] (b) tissue injury,[2] (c) altered bacterial flora.[1] Although Koch's postulates are, therefore, of little value in this instance, certain criteria, if fulfilled, would tend to establish the etiological relationship of these organisms to infantile diarrhea: (a) their demonstration by fecal culture in patients with diarrhea (evidence now available), (b) the demonstration of their disappearance in association with the cessation of diarrhea, and (c) the transmission of diarrhea by the administration of pure cultures of these organisms to human volunteers with their subsequent (but not prior) isolation in fecal cultures. It is the purpose of this report to present additional evidence in fulfillment of the first two listed criteria for the demonstration of a causative relationship between *Ps. aeruginosa* and proteus species and certain cases of infantile diarrhea, chiefly through the observation of the effect of polymyxin B on these organisms and the concomitant diarrhea in a group of four infants.

Many studies[2, 8, 10, 11, 12] have demonstrated the singular value of the polymyxins in vitro and in vivo in the control of *Ps. aeruginosa*. Similar studies[10, 11] usually demonstrate a moderate to extreme resistance of the proteus species to this drug. Report of the effect of the polymyxins on the enteritis associated with these organisms is limited to the use of polymyxin B in a single case of pseudomonas enteritis by Florman and Schifrin.[8] Thus, the apparently good response to

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polymyxin B of the enteritis associated with these organisms in three of the four included cases further extends the field of clinical usefulness of this drug.

MATERIAL

The four patients reported herein represent a small portion of an epidemic of diarrhea and vomiting of undetermined etiology prevalent in the community at the time of their observation. Approximately twenty-five seriously ill infants were hospitalized during a two-month period because of this condition and a far larger number were seen as outpatients. Because of the rapid intrafamily and intraward spread and the prevalence of the disease, it was assumed to be an infectious enteritis. Because of the lack of detection of abnormal fecal flora in any cases except those reported, it was presumed that the process was primarily due to a virus. The cases reported demonstrated unusual fecal flora only many days to weeks after the appearance of severe diarrhea, characteristic of the epidemic, and subsequent to the appearance of debilitating complications such as marked extracellular fluid loss, subarachnoid hemorrhage, and undernutrition.

Severe diarrhea and associated fluid and electrolyte imbalance of undetermined etiology is treated at this hospital by replacement of water, sodium, chloride, potassium, and vitamin deficits through a polyethylene tube inserted by venesection into an accessible vein or by subcutaneous infusion if no signs of circulatory insufficiency are apparent. Whole blood and plasma are frequently used (in three of the reported cases) when circulatory insufficiency is apparent. No antibiotics are used unless a parenteral infection or a stool pathogen is detected. Oral fluids are commenced as soon as circulatory insufficiency is corrected, but are limited to weak tea, glucose water, and skimmed milk until diarrhea has ceased.

Ps. aeruginosa and proteus species were detected in the reported patients only after one or more stool cultures had revealed only lactose-fermenting flora. Initial isolation was accomplished on thioglycollate, human blood, and SS agar as well as in selenite-F broth. Suspicious colonies were transferred to Kleigler's agar. The production of pyocyanin which distinguishes *Ps. aeruginosa* was proved by chloroform extraction. Sensitivity was determined by the inhibition of surface growth with a paper disk saturated in polymyxin B, 500 μg per cubic centimeter.

No distinctive clinical characteristics of this disease state associated with the presence of unusual fecal flora were detected. The varied changes associated with the fluid and electrolyte imbalance of the diarrheal state and the presence of other complications obscured any characteristic reactions of the host. However, when the disease state was essentially uncomplicated (and pseudomonas or proteus was present in the stools), fever tended to be low grade, the total white blood count was essentially normal with a relative increase in polymorphonuclear leukocytes, the stools tended to be frequent, yellow, and watery, with small amounts of mucus, and the child was listless and irritable. Daily urinalyses to detect the presence of renal damage consequent to polymyxin B were made, but, ex-

cept for the pyuria in Case 4 (presumably due to a Proteus urinary tract infection), no abnormalities were detected.

CASE REPORTS

CASE 1.—M. M., a 16-month-old white female infant, developed a moderate diarrhea consisting of six to eight watery yellow stools per day which required hospitalization of the infant and parenteral fluid therapy. She was placed on a reduced diet for approximately seven days after which the diarrhea subsided. Following an essentially asymptomatic five-day period, moderate diarrhea, vomiting, and fever reappeared, and six days later the infant again required hospitalization. Repeated stool cultures had revealed no enteric pathogens nor Pseudomonas, proteus, or paracolon bacilli. No evidence of parenteral infection was detected. Intravenous fluid therapy through a venesection was necessary for a three-day period to correct dehydration and restore electrolyte balance. Moderate anorexia, occasional vomiting, and continued diarrhea consisting of three to six large watery yellow stools waxed and waned though frank dehydration was prevented by the use of subcutaneous infusions. Low-grade fever, gradual decrease in weight from 16 pounds 7 ounces to 15 pounds 9 ounces, and lethargy persisted until the thirteenth hospital day when a stool culture revealed *Ps. aeruginosa* (sensitive to polymyxin B in vitro) for the first time. Polymyxin B, 4 mg., intramuscularly, every four hours was commenced. Diarrhea and fever subsided completely within forty-eight hours; weight rose from 15 pounds 9 ounces to 16 pounds 10 ounces in five days, and though a 400 c.c. subcutaneous infusion had been required the day prior to the start of polymyxin B, none was required thereafter. Diarrhea did not recur after the five-day course of therapy was completed and subsequent stool cultures failed to reveal *Ps. aeruginosa*.

CASE 2.—D. H., a 7-month-old white male infant, developed a severe diarrhea characterized by high fever and ten to twelve large watery yellow stools per day which required hospitalization of the infant on the fourth day of illness. No evidence of parenteral infection or abnormal stool flora was detected. Despite the replacement of fluid and electrolytes by daily subcutaneous infusions, evidence of peripheral and central vascular collapse, marked hyperpyrexia, and dehydration rapidly developed on the eleventh hospital day. Apparently complete correction was achieved by venesection and the continuous intravenous administration of fluids, electrolytes, blood, and Cedilanid. Continued severe diarrhea with low-grade fever required three additional venesections and intravenous alimentation for three- to six-day periods during the subsequent fifteen-day period. Rapid peripheral circulatory failure appeared within forty-eight hours of the discontinuance of intravenous fluids on the first three occasions, and though prolonged periods of oral starvation were utilized, diarrhea never ceased. Prophylactic penicillin was administered daily during this period to avoid respiratory complications. On the nineteenth hospital day *Ps. aeruginosa* (sensitive to polymyxin B in vitro) was isolated for the first time and was the predominating organism. Polymyxin B, 50 mg. every four hours, orally, was commenced and the diarrhea gradually subsided within six days, as the infant's weight rose from 14 pounds 3 ounces to 15 pounds 2 ounces. Polymyxin B was discontinued after ten days, but because of the reappearance of moderate diarrhea it was restarted three days later. Diarrhea ceased within twenty-four hours thereafter and did not recur nor was pseudomonas again detected in the stool.

Because of the absence of accessible veins, marrow infusions were utilized in both tibias. On the day oral polymyxin B was commenced bilateral tender hematomas were detected over

the sites of previous infusions. Incision and drainage revealed frank pus bilaterally which cultured *Ps. aeruginosa*. Sensitivity studies revealed that this organism was resistant to Chloromycetin, aureomycin, terramycin, penicillin, and streptomycin, but was completely sensitive to polymyxin B. Drainage with polyethylene catheters, curettage with streptokinase-streptodornase, and the intramuscular administration of polymyxin B, 4 to 10 mg. every four hours, achieved closure of draining sinuses and cessation of inflammation twenty-two days after onset. Radiological changes indicative of marked osteomyelitis in both tibias became apparent concomitantly with apparent healing of the subcutaneous abscesses. Continued therapy with intramuscular polymyxin B for a total of thirty-five days produced cessation of all bone destruction, and fifteen days thereafter sclerosis and progressive healing were proceeding satisfactorily. Subsequent observation has revealed apparently complete healing of the osteomyelitis clinically and radiologically. Mild oral moniliasis was noted during the latter part of polymyxin B therapy.

CASE 3.—M. H., a 4-month-old white female infant, developed moderate diarrhea of eight to ten watery green stools each day, with vomiting and fever, which required hospitalization of the infant and parenteral fluid therapy four days after onset. Diarrhea gradually subsided and the patient returned home on the fifth hospital day. Diarrhea, fever, and vomiting reappeared, necessitating rehospitalization five days later. Marked vomiting, anorexia, and lethargy with moderate fluctuating diarrhea and a temperature between 102° and 103° F. persisted throughout the hospital course. Despite almost daily subcutaneous infusions and continuous oral feeding, progressive weight loss from 13 pounds 1 ounce to 11 pounds 7½ ounces, increasing lethargy, irritability, and recurrent dehydration were apparent. No evidence of parenteral infection was detected and stool cultures revealed no unusual organisms until *Ps. aeruginosa* (sensitive to polymyxin B in vitro) was detected on the eighteenth hospital day. Polymyxin B, 50 mg. every four hours, orally, was commenced on the twenty-fourth hospital day at a time when marked anorexia, vomiting, and diarrhea consisting of four to six watery yellow stools per day had produced the first evidence of peripheral vascular insufficiency. Venesection and continuous intravenous alimentation were commenced at this time. Despite the cautious correction of plasma volume, marked tachycardia, liver engorgement, and cyanosis with severe vomiting and abdominal distention appeared. Diarrhea ceased as distention progressed. Despite Cedilanid, generalized edema, marked hepatomegaly, and jaundice appeared, and death ensued forty-eight hours after polymyxin B was commenced. Two species of paracolobactrum (in addition to pseudomonas) were isolated for the first time from the stool the day prior to death. During the last few days, oral moniliasis was noted.

Post-mortem blood culture revealed *Ps. aeruginosa*. Significant findings at necropsy were marked edema of the gastric mucosa, but complete absence of necrosis or ulceration of any portion of the gastrointestinal tract. The liver was moderately congested and revealed some areas of central lobular degeneration. Small patches of early meningitis were detected but organisms could not be discerned locally. No changes were detected in the myocardium. Many small hemorrhages in the adrenal cortex and marked lymphatic and thymus involution were apparent.

CASE 4.—L. F., a 6-month-old white male infant, developed a severe diarrhea consisting of ten to twelve large, watery, yellow mucous-containing stools per day which required hospitalization of the infant and the administration of parenteral fluids on the

fourth day of disease. Moderate diarrhea, vomiting, and anorexia persisted, but fluid and electrolyte balance was well controlled by repeated subcutaneous infusions. A spontaneous subarachnoid hemorrhage with focal convulsions, high temperature, stupor, and a residual left hemiparesis occurred on the fourth hospital day. The prolonged stuporous state required feeding by gavage for approximately two weeks during which moderate diarrhea and vomiting and persistent pyuria were present. *Proteus vulgaris* (sensitive to polymyxin B in vitro) was isolated from the stools and the urine for the first time on the ninth day of disease, two days after the subarachnoid hemorrhage. Repeated subcutaneous infusions were necessary to control dehydration, until the fifteenth hospital day when polymyxin B, 50 mg. every four hours, orally, was commenced.

Diarrhea gradually subsided, cleared seven days later, and no parenteral fluid was again necessary until three days after the tenth-day course of polymyxin B was completed. At that time diarrhea, vomiting, and dehydration reappeared, necessitating a second course of polymyxin B. Diarrhea and vomiting ceased within four days of the reinstitution of therapy and did not recur. Proteus was not isolated from either the feces or the urine after the second course of polymyxin B was commenced. No significant fever was noted after the reaction to the subarachnoid hemorrhage had ceased. A moderate oral moniliasis persisted throughout the latter part of polymyxin B therapy.

DISCUSSION

The cases reported corroborate the concept that the pseudomonas and proteus species have a relatively low invasive potential and that alteration of the host, chiefly by general debilitation, is necessary for infection to occur. In these cases the chief cause of the debilitation was diarrhea, presumably due to an unknown virus, an infection epidemic in the community and in other essentially identical cases unassociated with the presence of pseudomonas or proteus. These cases seem to demonstrate the possibility of enteral and systemic infection with these organisms secondary to an unrelated primary enteritis. The latter presumably subsides due to acquired host resistance while its original symptomatology is maintained by pseudomonas or proteus. The lack of antigenic activity of these organisms, demonstrated by several workers,[8, 13] presumably accounts for the chronic recurrent disease state noted in these cases, in contrast to the usual acute, self-limited course of infantile diarrhea. Persistent diarrhea (and debilitation) thus warrants repeated reevaluation by fecal culture to discover a possible secondary chronic enteritis associated with these organisms in which the lack of host reaction permits further debilitation, fluid and electrolyte alteration, and eventually fatal systemic invasion.

The appearance of pseudomonas and proteus in these cases after diarrhea and/or other complications had produced a state of diminished "resistance," and the persistence of diarrhea thereafter until the administration of polymyxin corroborates the previously demonstrated association of these organisms with diarrhea. (Positive stool cultures for pseudomonas species were found in thirteen of 3,000 normal specimens,[14] proteus species more frequently.) The apparent disappearance of these organisms from the stools in association with the cessation of diarrhea, presumably consequent to the administration of polymyxin B, is additional evidence suggestive of a

causative relationship between pseudomonas and proteus and infantile diarrhea. The simultaneous presence of active parenteral disease (osteomyelitis, pyelonephritis, and possibly meningitis) due to these organisms suggests that the concomitant enteral signs and symptoms were also due to pseudomonas or proteus.

The subsidence of prolonged diarrhea in association with the administration of polymyxin B in three cases and the relapse and subsequent renewed response after its discontinuance and readministration seem to indicate a definite effect of this drug upon the course of the enteritis as well as upon the organisms themselves. The response of the proteus urinary tract infection and the pseudomonas osteomyelitis, though not as prompt, seem equally definite. Indeed, the severe osteomyelitis present in Case 2 showed as rapid a response to polymyxin as would have been expected in the penicillin therapy of a streptococcal infection of bone. No renal or neurological (or other) toxicity of parenterally (or orally) administered polymyxin was detected in any case though Case 2 received between 3 and 8 mg. per kilogram of body weight per day intramuscularly for thirty-five days. The moderate oral moniliasis which was associated with polymyxin therapy was the only detectable complication and cleared rapidly when the drug was discontinued.

SUMMARY

1. Four cases of diarrhea in debilitated infants associated with the presence of pseudomonas and proteus are reported.

2. Observations are presented to support the thesis that these organisms may produce or prolong diarrhea in infants with pre-existing enteritis.

3. Polymyxin B seemed to have a beneficial effect upon the enteritis, pyelonephritis, and osteomyelitis due to these organisms in three of the four cases.

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TREATMENT OF ACUTE INFANTILE DIARRHEA WITH CAROB FLOUR (AROBON)

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ACUTE diarrhea, despite progress in therapy during the last decade, constitutes a major threat to infants and children. Because of the high morbidity and mortality, the diarrheas account for a large part of the pediatric ward admissions. In the state of California, infantile diarrhea ranked sixth among the leading causes of infant mortality in 1945.[1] In addition to the application of the basic principles of fluid balance and electrolyte metabolism in the management of diarrheal disorders, a constant search for substances that can be used to hasten the amelioration of symptoms has been going on. The efficacy of certain fruits in the treatment of diarrhea has been a matter of common knowledge for many years. The apple and banana have been tried and found to have favorable results and each has its advocates.[2]

In 1949 Smith and Fischer[3] reported the use of carob flour taken from the fruit of the carob tree, a leguminous plant which is native to the shores of the Mediterranean. This fruit (variously called St. John's bean, locust bean, Ceratonia siliqua) is a bean-shaped pod about 12 to 20 cm. long by 2 cm. wide. The pod contains a sweet pulp, rich in sugar (49 per cent) and low in protein (4 per cent) and very rich in lignin which is believed to be responsible for its unusual mechanical and detoxicating properties.

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The purpose of the present study was to determine whether the favorable results in the management of the diarrheas with the use of carob flour (trade name—Arobon) reported by Smith and Fischer[3] in 1949 and by Plowright[4] in 1951 could be confirmed by reviewing a larger number of cases.

CLINICAL MATERIALS AND METHODS

The General Hospital of Fresno County located in the center of the agricultural San Joaquin valley of California has admitted to its pediatric service an average of 455 cases of acute infantile diarrhea annually for the past five years (1947-1951). Since the latter part of 1949 the pediatric service has been using carob flour (Arobon) as an adjunct in the dietetic treatment of diarrheas. Over a thousand cases of diarrhea have been tried on the carob flour regime. Of this number 300 cases were selected, and for control, 300 patients treated previously (1948) on a similar regime but without Arobon. Cases of equal or similar severity were selected from both groups. The case histories, doctor's orders, course in the hospital, and duration of treatment were scrutinized in order to properly classify the diarrheas. Except for the addition of Arobon to the dietetic regime, the treatment was similar in both groups.

Because of the high costs of hospitalization, criterion for admission was generally as follows: (1) evidence of acidosis, (2) evidence of infection complicating the diarrhea, (3)

moderate to marked dehydration, (4) persistent vomiting accompanying diarrhea, and (5) failure to respond to treatment in clinic or outpatient department.

For convenient evaluation the severity of the patient on admission was classified as follows: (1) Mild—diarrhea with little or no dehydration with carbon dioxide combining power over 35 vol. per cent. (2) Moderate—diarrhea usually accompanied by fever, moderate dehydration, and with carbon dioxide combining power of from 25 to 35 vol. per cent. (3) Severe—diarrhea with extreme or marked dehydration, with carbon dioxide combining power below 25 vol. per cent, in moribund state or in extremis.

Of the 600 cases reviewed, 44 per cent fell under the classification of "mild" diarrhea, 34 per cent were of "moderate" severity, and 22 per cent were in the "severe" group. Although the carbon dioxide combining power is one of the few objective measurements of the severity of the illness, it was taken in only a small group (6 per cent), perhaps because of the fact that there were not enough trained personnel to handle this laboratory procedure and so only the most necessary ones were taken. Frequently, however, the severity index could be well defined clinically, i.e., the amount of acidosis is usually proportional to the amount of dehydration.

In all cases studied it was routine procedure to have stool cultures daily for at least three days after admission. For those that were positive for *Shigella dysenteriae* or of the Salmonella group, three negative stool cultures were reported before the patients were discharged. The usual admitting laboratory studies, as a complete blood count and urinalysis, were done.

Plan of Treatment.—The following is the regime used, the details modified according to the clinical symptoms, the duration, severity, and the objective laboratory findings:

I. *Period of Fasting:* It is usual to withhold all formula and oral medications for at least twelve hours, except in the mild cases without nausea or vomiting and where hunger is evident. If the child has not been vomiting, Ringer's-lactate or Hartmann's solution is given every hour in amounts of 1 ounce and gradually increased by ½ ounce until 3 to 4 ounces are tolerated.

II. *Feeding Plan:* Guided by the patient's demonstration of tolerance to oral feedings, the carob flour (Arobon) preparation is then given (in the proportion of one-half of 10 per cent Arobon with one-half boiled skimmed milk) in amounts according to the child's age. After the first formed stools, Arobon is then diluted with equal amounts of the "going-home formula," that is, one-half of 10 per cent Arobon and one-half of a 1:2 formula of evaporated milk. Then if the stools continue to be of satisfactory consistency, number, and volume, a straight "going-home formula" is finally given.*

III. *Parenteral Fluid Therapy:* As soon as possible fluids are given either intravenously or by hypodermoclysis depending upon the amount of de-

*A 10 per cent solution Arobon is prepared by adding 12 tablespoonsful to 32 ounces of water. Measure out Arobon into a dry pan and stir constantly while pouring 10 ounces of cool sterile water (boiled previously for 10 minutes) onto the Arobon. The remaining amount of sterile water (22 ounces) is brought to a boil, the Arobon solution added to it, and it is again brought to a boil. As soon as the boiling point is reached, remove the formula from the fire, allowing it to cool before pouring into the bottles.

TABLE I. SUMMARY OF DATA

	AROBON GROUP				NON-AROBON GROUP				MEAN-DIFF. OF TOTALS
	MILD	MOD.	SEV.	TOTAL	MILD	MOD.	SEV.	TOTAL	
Number of cases	126	108	66	300	138	96	66	300	
A. Comparable Data:									
Av. no. of days prior to admission	4.17	4.47	5.75	4.79	4.25	6.12	5.88	5.41	0.62
Av. no. of stools prior to admission	7.65	9.68	10.5	9.30	7.43	7.37	7.57	7.45	2.11
Per cent with bloody stools on admission	6%	15%	12%	11%	8%	8%	14%	10%	1%
Per cent with parenteral complications*	5%	9%	10%	8%	8%	15%	16%	13%	5%
Stool cultures:									
Positive Shigella	0%	9%	18%	9%	1%	6%	11%	6%	3%
Negative†	100%	91%	82%	91%	99%	94%	89%	94%	3%
									§*Standard deviation: 0.650*
B. Results:									
Av. no. of days before first formed stool	0.99	1.30	1.18	1.16	5.75	5.68	6.82	6.08	5.92
Av. no. of days before cure‡	3.91	6.15	7.85	5.97	8.14	8.84	10.52	9.18	3.21
Av. no. of days in hospital	5.13	8.28	10.8	8.08	9.81	11.3	13.05	11.41	3.33
Av. weight gain during hosp. (oz.)	10.9	9.0	23.1	14.0	8.7	8.02	12.9	9.87	4.43
Per cent of readmissions	6%	6%	9%	7%	12%	12%	15%	13%	6%
									§*Standard deviation: 0.612*

*As otitis media, URI's, pneumonia, etc.

†Proteus and coli-aerogenes group of microorganisms were cultured.

‡That is, the "going-home formula" was tolerated.

§Calculation for Standard Deviation[9]:

d—Mean difference.

Ed—Sum of d.

n—Number of values.

$\bar{d}$—Ed/n.

S^2d—Variance of single values—$E(d-\bar{d})^2/n-1$.

$S^2\bar{d}$—Variance of Means—S^2d/n.

$S(\bar{d})$—Standard Deviation of Means—$\sqrt{S^2(\bar{d})}$.

hydration, acidosis, or circulatory shock. The choice of fluids also depends to a great extent on the clinical picture. As soon as the dehydration and acidosis are corrected and when oral feedings are tolerated, parenteral fluids are discontinued in favor of the oral route.

Practically the same regimen was followed in the control group of 300 cases reviewed (comprising the period from January to December, 1948, before the use of Arobon was instituted in the dietetic therapy), except for the fact that in the feeding plan as soon as the infant's tolerance to oral feeding was evident, the formula was changed from Ringer's-lactate solution to boiled skimmed milk. This formula was kept up until stools became formed and the strength of the milk was gradually increased until the

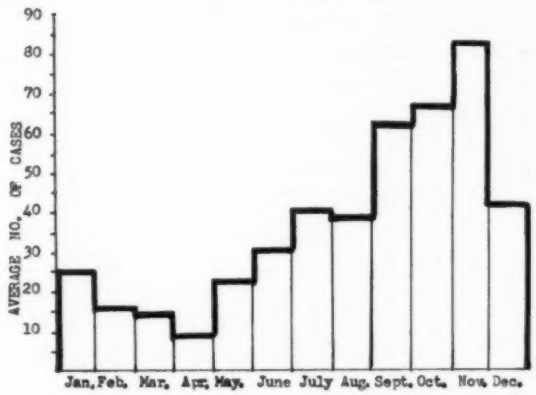

Fig. 1.—Seasonal incidence.

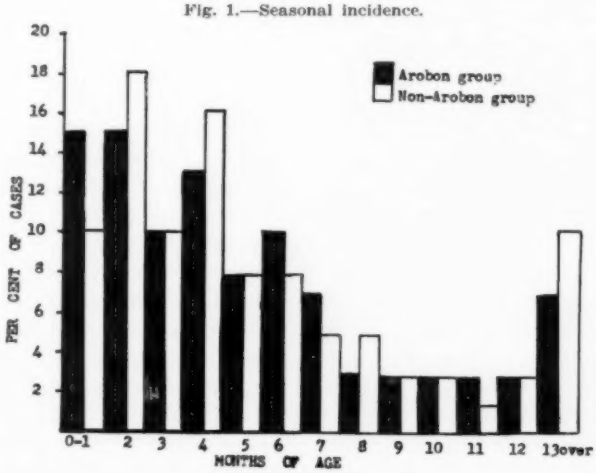

Fig. 2.—Age incidence.

IV. *Chemotherapy:* When the clinical picture or the results of the stool cultures and other laboratory studies indicate, antibiotics alone or in combination are used to control the infection.

child was on the "going-home formula."

RESULTS

Table I is a summary of the data collected from the two groups of cases. The data under subgroup A in this table shows quite a comparable course in both the Arobon and non-Arobon groups. There was 4.79 average number of days prior to admission in the Arobon group as compared to 5.41 days in the non-Arobon group. The Arobon group had 9.30 average number of stools prior to admission comparable to 7.45 average of the non-Arobon group. The percentage with bloody stools on admission together with the percentage of those with parenteral complications are still within the normal limits of deviation.

The data under Results show the differences in the results of the two groups. The Arobon group shows that formed stools are observed after an average of 1.16 days as compared to 6.08 days in the group without Arobon. It took only an average of 5.97 days before the "going-home formula" was tolerated in the Arobon group compared to 9.18 days in the non-Arobon group. Patients treated without Arobon stayed an average of 3.33 days longer in the hospital and had 6 per cent more readmissions. During their hospital stay the average weight gain of those on Arobon was 14 ounces compared to 9.87 ounces average weight gain of those treated without Arobon.

A definite seasonal incidence was noted (see Fig. 1). The lowest number of diarrhea admissions were during the months of February, March, and April. A gradual increase occurred during the summer, and the peak was reached during the month of November. An abrupt drop is observed during the cold months of December and January. Significantly, this seasonal incidence coincides with the seasonal migration of large groups of migrant laborers who work the vineyards and pick the cotton fields. Perhaps because of their economic handicap, ordinary sanitary conveniences and precautions are forgotten and proper care of their infants and children is wanting. It is from these workers in the rural areas that the main body of our patients comes.

The incidence of infantile diarrheas according to age in both the Arobon and non-Arobon groups is shown in Fig. 2. There is a comparable age incidence in both groups. There is a higher incidence in infants under 6 months (70.5 per cent) than in those over 6 months (20.5 per cent) of age. Only 9 per cent were children over one year.

DISCUSSION

Further review of the literature on carob flour reveals its use originally by Ramos and Ronzalen[5] of Spain during the Spanish Civil War. European pediatricians soon followed suit. Megevand and Riederer[6] reported favorable results in studies in Switzerland. Neyroud[7] and his colleagues from their studies in Bern concluded that the use of carob flour represents a considerable progress in the dietetic treatment of infantile diarrhea. Vianello[8] writing from the Pediatric Clinic of Bologna, Italy, confirmed its antidyspeptic properties.

It would seem that carob flour (Arobon) is effective in rapidly cutting down the number and improving the consistency of the stools and thus

preventing further electrolyte loss and metabolic derangement. Diarrhea patients tolerate simple carbohydrates and proteins well but fats poorly. Arobon, with its content of 49 per cent soluble carbohydrates (sucrose and reducing sugars) and 4 per cent proteins with only 0.5 per cent fats, provides a food which with its rich lignin and pectin content acts not only to detoxicate and constipate but also provides an adequate amount of calories (75 calories per ounce by dry weight).

On the point of acceptability to the patient, it was noted that those below 12 months took the formula containing Arobon contentedly. Three patients over 12 months of age refused the chocolate-colored Arobon solution. No evidences of toxicity or side effects were noted in the 300 patients on Arobon.

CONCLUSION

From the above studies, it would seem that the use of carob flour (Arobon) has been of considerable value as an adjunct in the dietetic therapy of infantile diarrheal disturbances, both in terms of shortening the period of hospitalization and shortening the duration of the disease. This does not, however, lessen the paramount role of the administration of fluids and electrolytes in the treatment of diarrheas.

SUMMARY

1. A study is presented of 600 cases of acute infantile diarrhea admitted to the pediatric service of the General Hospital of Fresno County. Three hundred of these cases were selected from those treated with carob flour (Arobon) as an adjunct in the dietetic therapy, while the other 300 cases were those patients treated without Arobon.

2. In a tabulated comparison the Arobon and non-Arobon groups present a similar picture. The results show significant statistical differences.

3. As an adjunct in the dietetic therapy of acute infantile diarrhea, carob flour (Arobon) is of considerable value in hastening cure and recovery.

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GENERALIZED CUTANEOUS HERPES SIMPLEX

Report of a Case Complicating Meningococcemia

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THE occurrence of localized herpes simplex infection, in the form of herpes labialis, complicating meningococcal infections is well known. Hoyne and Brown[1] have reported an incidence of 8 per cent in a series of 727 cases of meningococcal meningitis. This case is reported because it is an example of a rare occurrence, a generalized herpes simplex eruption.

Kaposi[2, 2a] in 1887 first described the vesicular eruption, which bears his name, in children who had pre-existing skin lesions of infantile eczema. It was not until 1941 that it was suggested that the virus of herpes simplex might be etiological,[3] and not until 1944 was the virus reported isolated from the lesions.[4] Since that time a number of confirmatory reports have appeared.[5, 6, 7, 8, 9] Two of these are worthy of special mention. In the paper of Barker and Hallinger,[5] one of the patients cited had no pre-existing skin lesions nor a history of eczema. In that patient, however, the lesions did not disseminate beyond the face and neck. In the report of Ruchman and Dodd,[6] in which seven cases are reviewed, one of the patients, while stated to have had a history of infantile eczema, is not specifically stated to have had pre-existing skin lesions at the time her Kaposi's varicelliform eruption developed. With these two possible exceptions no mention could be found in the literature of a proved generalized herpes simplex eruption occurring on an intact skin.

Other workers have recently demonstrated that vaccinia virus as well as herpes simplex virus may produce a clinical picture similar to that originally described by Kaposi as a varicelliform eruption (eczema herpetiforme),[10, 11, 12, 13] and leave the door open for the possibility of other viral agents likewise being offenders. In view of this finding it would seem wise, wherever primary virus isolation or complement fixation techniques are available, to classify varicelliform eruptions in accordance with the etiological virus. This procedure was adopted here.

CASE REPORT

D. P., a 7-year-old white female, was admitted to the pediatric service of Baltimore City Hospitals on March 25, 1950, because of fever, coma, and skin rash of a few hours' duration. The family history revealed only that the father was suffering from multiple sclerosis. There were no allergic or skin diseases present in any other member. The past history was significant in that she had had infantile eczema at the age of 4 months which had persisted to the age of 14 months. She had been hospitalized at another hospital for a four-month period during this illness. After the age of about 14 months, however, it was said by her family that there had been no recurrent skin lesions. At the age of 5 years a diagnosis of rheumatoid arthritis was made, also at another hospital, and the patient spent several months in a convalescent home. Except for an attack of pertussis in November, 1949, she had been essentially well during the six months prior to admission.

The acute illness began the morning of the day of admission, with drowsiness and lethargy. By afternoon it was noted that she was feverish. Finally about an hour before admission it was noted that she was delirious and was developing a skin rash.

From the Department of Pediatrics, Baltimore City Hospitals.

Fig. 1.—Photograph showing the dissemination and localization of some of the lesions forty-eight hours after appearance.

Fig. 2.—Close-up revealing details of the lesions.

On admission she was found to be a slender girl weighing 40 pounds, and she was comatose. The temperature was 106° F., pulse 180, respiration 42, and blood pressure 110/70. Fresh petechial hemorrhages were present in the skin and mucous membranes, and subconjunctival hemorrhages were also noted. There was a soft systolic murmur heard over an otherwise normal heart. There was slight nuchal rigidity and the Kernig sign was positive. The remainder of the examination was not remarkable.

Laboratory Data.—The admission urinalysis showed a trace of albumin and an occasional white cell and granular cast in the centrifuged sediment. The blood showed 4.1 million red blood cells, 12.5 gram hemoglobin, 4,200 white blood cells; 80 per cent of the white blood cells were of the polymorphonuclear series. The erythrocyte sedimentation rate equaled 22 mm. per hour, corrected by the Wintrobe method. Serum analyses revealed essentially normal electrolytes and urea nitrogen content on two occasions. Blood culture obtained on admission grew *Neisseria meningitidis* (intracellularis). Spinal fluid showed 25 mononuclear cells per cubic millimeter, glucose 100 mg. per cent, protein 25 mg. per cent, chloride 126 meq. per liter. Culture was sterile. *N. meningitidis* was recovered from throat culture.

Course.—The patient was given 1 Gm. of sodium sulfadiazine intravenously and 1 Gm. subcutaneously stat and 1 Gm. every six hours. In addition she was started on penicillin 30,000 units every three hours. She exhibited a definite reduction of fever within eight hours. In the morning, however, examination revealed much more marked meningeal signs than on admission and it was felt clinically that she had meningitis. No additional lumbar puncture was done, however, inasmuch as the patient was obviously improving. So far as her primary disease was concerned she continued a favorable course and after admission never again had a temperature beyond 101.4° F. and was entirely afebrile from the eighth day until discharge on the fourteenth day. The morning after admission she was no longer delirious and she became rational and alert within thirty-six hours.

On March 27, 1950, the patient developed the typical vesicular lesions of herpes labialis (simplex). The following day the vesicular lesions on an erythematous base had become disseminated over much of the body, involving both the dorsal and flexor surfaces of the elbows and knees and also involving the buttocks and thighs. These lesions continued to spread for the next seventy-two hours and then spontaneously subsided. At no time did the eruption seem to cause the patient a significant degree of discomfort. The subsequent course of the patient was uneventful. At no time during the period she was observed were any eczematoid lesions seen.

Herpes simplex virus was isolated from vesicle contents in the following manner*: Fluid was aspirated from three vesicles located in different regions—the right hand, the left arm, and the right leg. Each of these specimens was inoculated onto the chorioallantoic membrane of three 11-day-old chick embryos. One membrane from each set was then reinoculated for a second passage on chorioallantoic membranes. From this second passage material descended from each of the parent vesicles was inoculated onto the cornea of a rabbit. Each rabbit developed a keratitis and subsequently withstood a challenge inoculation of the usually fatal HF strain of herpes simplex. Finally, after a third egg passage, membranes containing material descended from each of the original inocula were sectioned and stained. All three preparations were found to contain the intranuclear inclusion bodies typical of herpes simplex. Thus by both

*We are indebted to Dr. Frederik B. Bang, of the Department of Medicine of the Johns Hopkins University School of Medicine and Hospital, who isolated the virus.

rabbit cornea inoculation and tissue section, the virus had the characteristics of herpes simplex.

DISCUSSION

It is noted that in this patient a generalized eruption caused by herpes simplex virus occurred on an apparently intact skin. Ordinarily such eruptions occur on a skin that is presumably rendered more susceptible by another disease, usually infantile eczema. One might speculate that the prior occurrence of infantile eczema in the above case might have been the time of an initial invasion by the herpes simplex virus (unnoticed, unremembered, or perhaps not clinically manifest) which "sensitized" the skin for a subsequent attack. This attractive hypothesis cannot be validated by the available data but might be tested by complement fixation studies should another such case present itself.

SUMMARY

A case of generalized cutaneous eruption caused by the herpes simplex virus, complicating meningococcemia, and occurring in apparently intact skin has been presented. The significance of this apparently rare phenomenon has been discussed against the framework of recent developments relating to the etiology of Kaposi's varicelliform eruption.

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CONGENITAL HYPERTROPHIC PYLORIC STENOSIS IN A SMALL PREMATURE INFANT

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HYPERTROPHIC pyloric stenosis is uncommon in small premature infants. While no statistics as to incidence are available, a review of the English literature reveals four cases in premature infants, born five weeks or more prematurely, which have been successfully treated surgically. Weeks and Brooks[1] reported a case in a 3 pound 12 ounce infant operated on at the age of 6 weeks. Gallagher[2] reported an operation on a 3 pound 8 ounce infant at the age of one month. He also reported a communication from Ladd on a 3 pound 14 ounce infant operated on at the age of one month. Vickers and Conrad[3] reported an operation on a 3 pound 12 ounce infant at the age of one month. We report below a case of hypertrophic pyloric stenosis in a 6-week-old 4 pound 2 ounce premature infant successfully treated by surgery.

CASE REPORT

A male infant, born at home after 7 months' gestation, was admitted to the pediatric service of Wyckoff Heights Hospital on June 25, 1951. Birth weight was 3 pounds 14 ounces. On admission, the infant's color and respiration were good and there were no unusual physical findings. The baby was placed in an incubator. After twenty-four hours, glucose water feedings were begun and were followed the next day by a Similac formula. Although the baby took the formula well and no regurgitation or vomiting was noted, he slowly declined in weight to 3 pounds 6½ ounces on July 5. His formula was changed to half-skimmed milk with added carbohydrate (Dalactum). He gained rapidly and by July 29 weighed 4 pounds 5½ ounces. After the infant was a week old, 0.3 c.c. of an aqueous multivitamin preparation and 25 mg. of additional ascorbic acid were added to his formula daily.

On July 29, the baby suddenly vomited his 6:00 P.M. feeding. Every feeding that night and the next morning returned and vomiting was noted between feedings. Physical examination on July 30 disclosed nothing unusual. The baby's abdomen was soft and flat. No masses were felt and no peristaltic waves were observed. A chest roentgenogram disclosed no changes referable to either pulmonary fields or to the mediastinum. The heart was normal in size and position. The urine was normal. A blood count disclosed hemoglobin 14.5, red blood count 4,330,000, white blood count 10,800, polymorphonuclears 48, lymphocytes 52. Despite the absence of fever or other objective signs of an inflammatory reaction, it was believed that the infant's vomiting was probably secondary to an infection and intramuscular penicillin therapy was instituted. Feedings were discontinued and fluids administered subcutaneously and intravenously. The vomiting subsided and small glucose water feedings were cautiously reinstituted on July 31. With the resumption of feedings, the baby resumed vomiting. Penicillin was discontinued and intramuscular chloramphenicol therapy was instituted without any visible change in the infant's condition. Although the vomiting was not projectile at any time, the vomitus had now become dark brown in color. The possibility of intestinal obstruction was considered. An abdominal roentgenogram taken on July 1 disclosed considerable air in the stomach but no gaseous content in either the small or large bowel. Me-

From Wyckoff Heights Hospital of Brooklyn.

chanical obstruction at the pylorus was suspected. The surgical consultants felt that hypertrophic pyloric stenosis was the probable cause of the infant's vomiting, despite the atypical clinical picture. It was believed that since the baby was still in good condition, surgical exploration was warranted.

On August 2, under rectal pentothal and procaine local anesthesia, a high right rectus incision was made and the abdomen entered. Collapsed small bowel protruded into the wound. The stomach and duodenum were located high under the liver, which was dark red and extended to the umbilicus. The stomach was dilated. The pylorus and adjacent duodenum and stomach were thickened, blanched, and edematous. The pylorus was enlongated and had a hard consistency. It measured about 1.2 cm. in diameter. The small bowel appeared completely collapsed.

A 2 cm. incision was made longitudinally through the anterior superior portion of the pylorus and adjacent duodenum and stomach. The muscle layers were spread until mucosa pouched freely through the gap and the constricting ring appeared relieved. The baby left the operating room in good condition.

Following the operation, the baby was given a transfusion of 40 c.c. of whole blood and intravenous glucose and saline were continued. A small amount of potassium chloride solution (30 c.c. of 1:100 solution) was given subcutaneously. After twenty-four hours, feedings were started with small amounts of glucose water and the volume was gradually increased with each feeding. A dilute half-skimmed milk formula with added carbohydrate (Dalactum) was offered after another twenty-four hours. This formula was rapidly concentrated and gradually increased in volume. There was neither vomiting nor regurgitation following the operation. The infant gained rapidly from 4 pounds 7 ounces on August 3 to 5 pounds 5 ounces on August 19. The child was discharged on August 20.

The child was seen in the clinic on April 23, 1952. He is well nourished and weighs 22 pounds. The mother states that he tolerates a full diet and presents no unusual feeding difficulties.

DISCUSSION

There were several features of the clinical picture that were atypical of pyloric stenosis. The onset was sudden rather than gradual; visible peristaltic waves were absent; and no pyloric tumor was palpable. A roentgenogram of the abdomen disclosing no air in the gastrointestinal tract beyond the pylorus is also atypical. Of the cases of hypertrophic pyloric stenosis in small premature infants reported in detail in the literature, the case of Vickers and Conrad[3] presented a clinical picture somewhat similar to our case. However, the cases of Weeks and Brooks[1] and the case of Gallagher[2] had the symptoms and signs considered characteristic of pyloric stenosis. Since surgical treatment of hypertrophic pyloric stenosis is obviously feasible in premature infants, the possibility of its occurrence even in the presence of somewhat atypical symptoms should be kept in mind.

SUMMARY

A case of hypertrophic pyloric stenosis occurring in a 4 pound 2 ounce premature infant successfully treated surgically is reported.

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DUPLICATION OF THE ALIMENTARY TRACT

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THE gastrointestinal tract is a fertile field for various and curious malformations providing a fascinating study for both surgeons and pathologists. These malformations[13] have been described as enterogenous cysts, enteric cysts, ileum duplex, giant diverticula, inclusion cysts, and duplication of the alimentary tract. The latter term is all-inclusive and is preferred. Duplications[5] are spherical or elongated hollow structures composed of smooth muscle lined by mucous membrane and intimately attached to some portion of the alimentary tract. Usually there is fusion of the external musculature with a common serosa[6] and a common blood supply. The duplicate segment may or may not communicate with the normal lumen. Although this anomaly may appear at any level from the base of the tongue to the anus, it is found more frequently in relation to the small intestine.[16] These duplicated organs are found in the mesenteries, in retroperitoneal spaces, and within the wall of the viscus.

Duplication, as defined previously, may develop and persist under the influence of the organizer hormone. During the development of the intestinal tube a solid stage occurs. Small vacuoles have been observed, and the lumen results from their coalescence.[14] Incomplete obliteration of the partition could give rise either to a duplicate or triplicate bowel. On the other hand, diverticula of the intestine have been observed in the 22.8 and 30 mm. embryo.[6] These are thought to migrate or develop in the mesentery giving rise to the duplicated segment. Communication with the parent bowel may persist or may be obliterated.

Duplication is a rare anomaly, and one may never encounter this lesion in surgical practice. Ladd and Gross[13] report eighteen duplications in their series. A double gall bladder[15] occurs about once in 3,000 to 4,000 people. Twelve duplications[11] and one triplication[8] of the colon are reported in the world's literature and at least two cases of duplication of the appendix[9, 11] are reported.

The symptoms of duplication of the bowel depend on location, size, degree of obstruction, degree of impairment of blood supply, and the presence of mucosal ulceration. Although no symptoms may be present, usually vomiting, diarrhea, melena, colicky pain, and/or symptoms of peritonitis may be present. The physical signs include the presence of an abnormal movable mass, alteration of peristalsis, abnormal areas of dullness or resonance. X-ray examination may reveal abnormal gas and fluid shadows which might lead one to suspect this condition. In one case[9] the correct preoperative diagnosis was made by barium enema. Abnormal displacement of intestine may also suggest this lesion. The complications encountered include: hemorrhage, ulceration, vascular obstruction, perforation, intussusception, mechanical obstruction, closed loop obstruction, and fistula formation.

The correct preoperative diagnosis is seldom made. The patient is usually treated for a surgical emergency such as hemorrhage, intestinal obstruction, intussusception, or peritonitis. The differential diagnosis[5] must exclude Meckel's diverticulum, polyp, dermoid, mesenteric cyst, urogenital cyst, teratoma, hydatid cyst, pancreatic cyst, polycystic kidney, appendicitis, and intussusception. Other congenital anomalies will be present in a high percentage of these patients.

When duplication is found at operation, a major surgical procedure will be required. Fisher[7] recommends the immediate introduction of a polyethylene tube into the saphenous vein, prompt correction of electrolyte im-

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balance, and restoration of blood volume. If possible, the entire abdomen should be carefully explored first and decision deferred until this has been completed. In general, the treatment of choice is surgical excision[1, 7, 13, 15] with restoration by side-to-side, end-to-side, or end-to-end anastomosis. The duplicated segment usually cannot be dissected from the bowel because it is densely adherent and is supplied by common vessels. Attempt at local excision usually results in perforation of the viscus and destruction of blood supply. In such lesions as duplication of the colon or stomach a communication[7, 16] may be accomplished by simply breaking down the spur. If resection is not feasible, drainage may be provided by marsupialization.[7] The mucous membrane should then be destroyed by pack or escharotics.

CASE REPORT

A 3-month-old male infant was admitted to the hospital on Oct. 29, 1951, because of vomiting of four hours' duration. The patient was first seen in the home after having vomited three times in the previous four hours. There had been a normal bowel movement twelve hours before admission. The infant had previously been in good health and had never had any gastrointestinal disturbances.

Upon admission, the patient appeared listless, but could be aroused by stimulation. The skin was clear and well hydrated. The rectal temperature was 99.8° F. There was no local or general lymph node enlargement. Both eardrums were intact and normal. The nasopharynx was normal in appearance. The pupils were round, regular, equal, and reacted to light. The lungs were clear to percussion and auscultation. The heart sounds were rapid, regular, and no murmurs were heard. Upon palpating the abdomen, a firm movable mass was felt in the right abdomen, lateral to the umbilicus. The mass was 4 × 2 cm. in size, and was tender. There was no distention, and peristalsis was hyperactive. There were no other palpable masses or viscera. The genitalia were normal. Rectal examination revealed no palpable mass or blood on the examining finger. The remainder of the examination was essentially negative.

The routine blood and urine examination was within normal limits. Roentgen examination of the abdomen showed the usual amount of intestinal gas. There were no taut or distended loops of bowel, and no evidence of intestinal obstruction seen.

It was felt that an early intussusception was present, and a laparotomy was performed ten hours after the onset of vomiting. Upon opening the abdomen and delivery of the terminal ileum and cecum, a cystic mass was seen 1 cm. proximal to the ileocecal valve. The mass measured 4.5 × 3 × 2.8 cm. in size, and had produced extrinsic obstruction to the lumen of the ileum. Numerous fairly soft nodes measuring approximately 4 to 8 mm. in size were present in the mesentery of the ileum. By sharp dissection an attempt was made to outline a cleavage plane in the superior and inferior portions so that the tumor could be shelled out and thus preserve the continuity of the bowel. No cleavage plane could be developed, and it was presumed that the tumor mass was made up of the wall of the intestines. The mass was resected and an end-to-end anastomosis was performed.

The patient was given nothing by mouth for three days following surgery, and during this time was given fluids by vein. Oral feedings were begun on the fourth day and were taken without vomiting. The postoperative course was uneventful and the patient was discharged on the tenth hospital day.

Pathological Examination.—The specimen consists of a mass 4.5 × 3 × 2.8 cm., along one surface of which runs a segment of small bowel 4.3 cm. in length. The lumen of the small bowel can be probed with a blunt probe but it is markedly compressed by a tense ovoid mass over which the bowel is stretched. On opening this mass it is seen to be a cyst, lined by gray-white tissues, and show-

ing a wall averaging 2.5 mm. in thickness. The wall is made up chiefly of a hypertrophied muscle layer. The lining is smooth and glistening. The segment of bowel shows an intact, gray-tan mucosa, and the portion of the cyst wall directly adjacent to the bowel apparently has no muscular coat, the wall being composed entirely of the mucosa of bowel and the lining of the cyst. Moderate hypertrophy of the bowel wall is present, the wall averaging 3 mm. in thickness.

Microscopic examination of the sections of the cyst shows it to be lined by a poorly developed small intestinal-type mucosa, with a loose, edematous-appearing tunica propria, infiltrated by fairly numerous round cells. The submucosa is not remarkable but the muscular layers, both circular and longitudinal, show marked hyper-

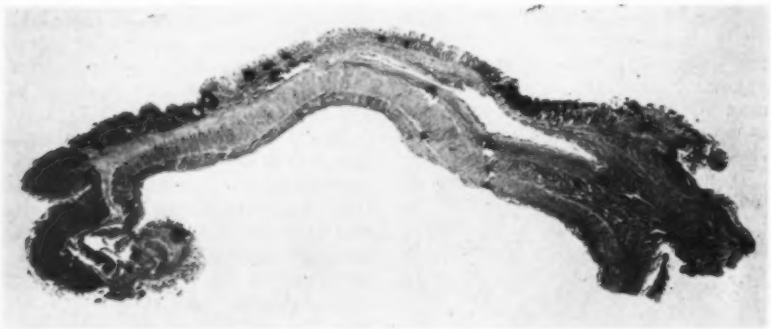

Fig. 1.

Fig. 2.

Figs. 1 and 2.—Depicting the lumen of the duplicate segment lined by columnar cells of intestinal type. The common muscularis can be seen adjacent to the submucosa of the duplicate cyst and the submucosa of the intestinal lumen.

trophy of the fibers. Portions of the cyst lack a lining and other portions show a simple columnar epithelium lining them. The wall of the intestine adjacent to the cyst shows a relatively normal mucosa, with wide infiltration of the tunica propria by polymorphonuclear leukocytes, round cells, and some hemorrhage. The muscular coat is present but is poorly formed and quite thin. The cyst lining adjacent to this portion of the wall is infiltrated by numerous leukocytes. The wall away from the cyst shows hypertrophy of the muscular layer and numerous lymphatic follicles and round cells are seen within the tunica propria.

Pathological Diagnosis.—Congenital anomaly of the ileum, and duplication of the small bowel, producing a cyst, with high-grade compression and obstruction of the ileum with acute and subacute inflammation of the ileum and cyst.

DISCUSSION

Vomiting in infancy is a very common complaint and frequently a diagnosis of intestinal obstruction is not made until tympanites and obstipation occur. When this is present, the accompanying distention, dehydration, and toxicity increase the surgical risk, make preoperative correction of these abnormalities mandatory, and create a grave prognosis in infants. For these reasons, an early diagnosis is essential. The most important single factor in establishing an early diagnosis is the physical examination of the abdomen. Anyone who examines these babies must be willing to spend time to perform satisfactory palpation of the abdomen. This requires great patience and skill, since the child is frequently crying and in distress. Mechanical intestinal obstruction due to duplicate bowel, intussusception, or any other mechanism requires prompt diagnosis and prompt institution of corrective measures. The responsibility for making an early diagnosis and the subsequent decrease in infant mortality from surgery rests entirely with the pediatrician or the family physician.

SUMMARY

1. A duplication of the ileum causing obstruction in a 3-month-old infant is reported with recovery following an intestinal resection of the lesion.

2. The incidence, etiology, and treatment of duplication of the bowel are discussed.

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HYPERVITAMINOSIS A

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SINCE 1944 when Josephs[1] first reported the syndrome of hypervitaminosis A in man, reports have appeared with increasing frequency until at present twenty-three such cases are recorded.[1-13] Briefly, the components of the syndrome[5] in children are: cortical thickening of the involved long bones with pain and swelling over them, hyperirritability, pruritus, rash, cheilosis, changes in the hair ranging from coarseness to alopecia, and, on occasion, bleeding tendency. The diagnosis is established by finding an elevated serum vitamin A level.

CASE REPORT

W. M., a 24-month-old female, born on March 4, 1950, was seen on Feb. 27, 1952, because of skin rash, hyperirritability, and forearm tenderness. The patient had been well until the age of 14 months, when she became bowlegged. Films of her legs and arms, at 16 months, showed only slight bowing of the tibias (Fig. 1). At 18 months, she lost her appetite and failed to gain weight. Approximately three weeks later, a generalized itchy rash appeared which was more marked on the extensor surfaces of the extremities. Hyperirritability was noted at 21 months. At 22 months, an orthopedic surgeon suspected early tibia vara,[14] prescribed corrective shoes, and told the parents to "Give the youngster an adequate vitamin intake." At this time, the child's legs and feet were exquisitely tender. One month later, this tenderness had subsided, but her forearms had become painful. Fever, hair changes, cheilosis, or hemorrhagic manifestations never were apparent.

The patient was a first-born child, delivered normally at term. Early growth and development were normal prior to the fourteenth month.

Feeding History.—The infant was breast fed until the age of 6 months when she was changed to formula. Orange juice was started at age 2 weeks, one ounce daily. This was gradually increased until at 18 months she received eight ounces daily. Oleum Percomorpheum* was started at 3 weeks, four drops a day. This was continued until age 3 months when the dose was increased to six drops a day. At 7 months, the child was given ten drops daily. This was continued until age 18 months, when the dose was increased to four droppersful (120 drops) daily. At 22 months, the dose was increased to eight droppersful, which was continued until the twenty-fourth month. The mother stated that she increased the dose on her own initiative in the hope of improving her child's appetite.

Physical examination revealed a very irritable, uncooperative and slightly undernourished 24-month-old female child who complained bitterly when her forearms were touched. The skin over the anterior surfaces of the arms, legs, buttocks, and lower abdomen was dry, coarse, and scaly, and had numerous scratch marks. The forearms presented long, spindle-shaped swellings on the lateral surfaces of the ulnas. The swellings were of bony consistency, and were attached to the bone; the overlying skin was freely movable. The tibias were bowed, but were not tender or swollen. The child was afebrile; the head was symmetrical, with no frontal bosses or mandibular swelling. The hair was normal in

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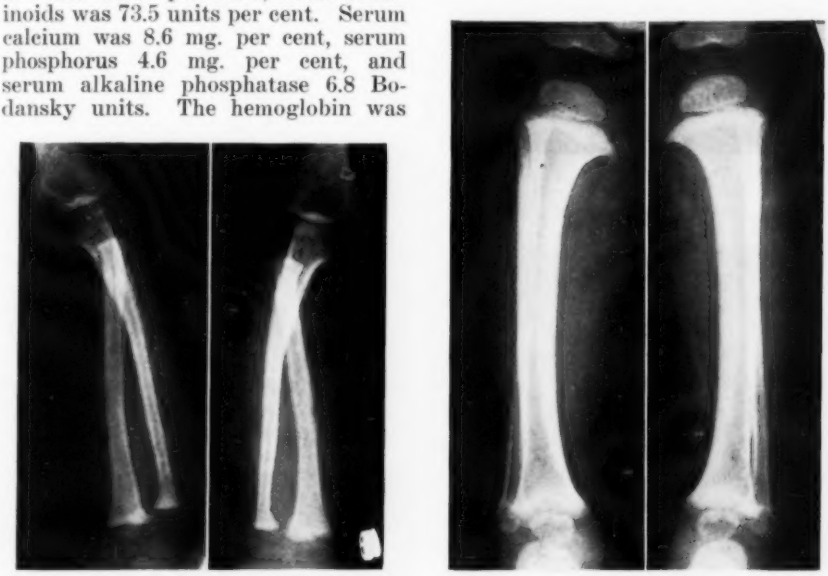
*One drop of Oleum Percomorpheum contains 1,250 units of vitamin A and 180 units of vitamin D.

texture. Sixteen normal teeth were present. The upper respiratory tract, heart, and lungs were normal. The liver was palpable one fingerbreadth below the costal margin. The abdomen was normal.

Laboratory Findings.—On Feb. 27, 1952, the serum vitamin A level was 100 blue units per cent—normal 10 to 20;[15] total carotinoids was 80.0 units per cent—normal 50 to 100. On March 6, one week after vitamin A was discontinued, serum vitamin A level was 20 blue units per cent; total carotinoids was 73.5 units per cent. Serum calcium was 8.6 mg. per cent, serum phosphorus 4.6 mg. per cent, and serum alkaline phosphatase 6.8 Bodansky units. The hemoglobin was 11.0 grams, red blood count 4.1 million, white blood count 8,800; the differential count was 59 polymorphonuclear cells, 3 monocytes, and 38 lymphocytes. Urine contained 7 to 10 white blood cells per high-powered field, and one-plus albumin. Subsequent catheterized urine specimen had no albumin or cells. On March 18, cephalin flocculation test was negative, thymol turbidity was 1 unit, and serum bilirubin was 0.015 mg. per cent. Total serum protein was 8.4 grams per cent, serum albumin 5.4 grams per cent, and globulin 3.0 grams per cent.

Roentgenographic Findings.—In February, 1952, roentgenographic examination of the entire skeleton disclosed bilateral symmetrical cortical thickenings of the ulnas, the anterior surfaces of the tibias, and the second to fifth metatarsals (Fig. 2 *A-C*). The cortical thickenings were most prominent in the ulnas where the distal two-thirds of the shafts were affected. The changes in the ulnas corresponded exactly to the tender swellings in the forearms. The skull, mandible, clavicles, vertebrae, fibulas, and the remainder of the long bones were not involved.

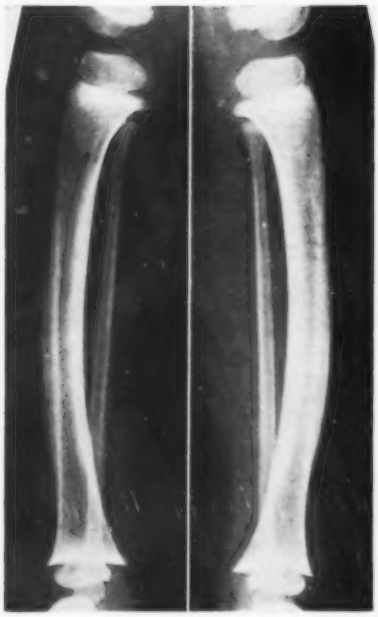


A. *B.*

Fig. 1.—Roentgenograms at 18 months of age, before the ingestion of excess quantities of vitamin A. *A*, The radii and ulnas appear normal. *B*, The tibias are slightly bowed and demonstrate the structural changes usually associated with bowing, i.e., thickening of the concave side.

Clinical Course.—Immediately after the diagnosis was confirmed roentgenographically, all intake of Oleum Percomorpheum was discontinued. Forty-

A.



B.

C.

Fig. 2.—Roentgenograms at 24 months of age, after the ingestion of toxic quantities of vitamin A. *A*, Bilateral symmetrical cortical thickening of both ulnas is present. *B*, The tibias are thickened anteriorly. *C*, Bilateral symmetrical cortical thickening of the shafts of the second to fifth metatarsals is demonstrated.

eight hours later, hyperirritability and bone tenderness were greatly diminished; after seventy-two hours, the pruritus was considerably relieved. Within seven days after discontinuing vitamin A, tenderness, hyperirrtability, and pruritus were barely perceptible, and the rash had begun to clear. After fourteen days, the child was asymptomatic, and the rash was almost completely cleared. This child was treated on an outpatient basis during the entire clinical course.

COMMENT

The striking clinical features of this patient—hyperirritability, rash, and swelling of the ulnar aspects of the forearms—suggested the diagnosis of hypervitaminosis A immediately. Specific inquiry regarding the use of vitamin preparations elicited the history of excessive ingestion of Oleum Percomorpheum.

We were able to obtain quick roentgenographic confirmation of the diagnosis, and felt that hospitalization was unnecessary while awaiting the result of the blood vitamin A level determination. Treatment at home consisted of withdrawal of vitamin A and application of calamine lotion. The

quick return to normal of the serum vitamin A level is unusual. We were fortunate in having films taken before the ingestion of excessive vitamin A (Fig. 1). They serve to demonstrate graphically the marked selective bony changes which this disease is capable of producing.

With increasing awareness of the clinical entity of hypervitaminosis A,[16] cases are being recognized and diagnosed with greater frequency. We are reporting this case to supplement the statements already made regarding the potential toxicity of vitamin A and the desirability of proper safeguards being adopted in labeling all preparations containing vitamin A. The label should state the proper dose and warn mothers of the danger of overdose. It is appropriate at this point to note that the increased vitamin D intake usually accompanying excess vitamin A ingestion is not believed to be a pathogenic factor.[8, 11] Furthermore, this child manifested no symptoms or signs usually associated with hypervitaminosis D.[17]

CONCLUSIONS

1. An additional case of chronic poisoning due to the excessive administration of vitamin A is reported.

2. Further evidence of the necessity of proper labeling of the many easily available and commonly used vitamin A preparations is presented.

3. Prompt recognition and early diagnosis of this condition will avoid unnecessary hospitalization and expense.

We wish to express our appreciation to Dr. John Caffey who has reviewed our films and found them similar in every respect to the previously reported cases.

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Medical Progress

CHEMICAL GROWTH IN INFANCY AND CHILDHOOD

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THE particle of matter is no longer considered as a determinant, but as a conditioner of physiological or biochemical reactions whose nature and possibilities are just beginning to be realized. Somewhat appalling as it is, we face the necessity of rejecting most of the explanations of life and heredity based on morphological grounds and building anew, practically from the beginning, on a physiological basis."[9]

Moulton first spoke of "chemical maturity" in 1923.[51] From the time of von Bezold, a century ago, it has been realized that the bodies of young animals, including man, differ quantitatively in chemical composition from the adult of the species. Relatively little emphasis has been placed on this aspect of human growth, however: embryological researches, so important for the understanding of the pathogenesis of congenital anomalies, and studies of the relation of organ and total body mass to age have demanded so much of the biologist and pediatrician that the more difficult subject of chemical growth has suffered by comparison. Developments in the field of mental and emotional growth have also occupied the attention of the clinical investigator.

Three hundred years elapsed between the age of Vesalius and that of Liebig, and eighty more to Shoenheimer's "Dynamic State." Modern medicine is gradually undergoing a change from the morphological to the functional point of view. Disease processes are being described more frequently in physiological and biochemical terminology. Mass connotes a static system, chemical processes are dynamic; and life is chemical. The answer to the question: "The dead body of a squirrel is not a squirrel and we know not why, but there is no reason to despair the answer"[9] must necessarily carry the investigator far beyond the realm of morphology.

Behaviorally and morphologically the child is not a miniature adult. It is the purpose of this review to emphasize that from the quantitative chemical standpoint growth is accompanied by changes in body composition. The subject of chemical embryology got under way some twenty years ago with the publication of Needham's[52] classic treatise. Intensive work is in progress relative to the biochemistry of the ageing process and the growth of tumors.

Although an abundance of information exists on the subject of the differences in chemical composition between child and adult, systematic studies of rates of change during the growth period are considerably fewer in number. Macy has been very active in this field for many years, and her monumental three-volume work on *Nutrition and Chemical Growth in Childhood*[44] contains much valuable information based on results of extensive meta-

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bolic balance studies in growing children. Shohl's observations were brought together in book form in 1939, and his monograph serves as a complete review of the subject of mineral metabolism.[62] Stearns' contributions in this field are well known.[66] The British workers, notably Widdowson and McCance and their collaborators, are currently engaged in a re-examination of some of the earlier concepts of chemical growth.

No attempt will be made here to discuss the chemistry of the growth process per se, nor will this review touch on the fundamental question of growth as a biochemical phenomenon. Rather, we shall be concerned with the chemical composition of postnatal human growth. With but few exceptions, only data collected successively over a well-defined segment of the growth period will be included. Matters of prime concern to the physiologist, such as renal function, blood volume, cardiac output, and the like, will not be considered. Information relative to the fetus will be included where pertinent.

TOTAL BODY COMPOSITION

Data on fetal composition for the entire range of intrauterine development have been accumulating during the past years. A sufficient number of newborn infants have been analyzed by direct chemical methods to render our knowledge of this particular age group rather complete. The method of choice for the determination of total body composition, namely, carcass analysis, is obviously of extremely limited applicability in postnatal man. Most of the postnatal subjects analyzed to date cannot be considered as completely representative of a normal human being. The subject of Mitchell and associates[49] was a 35-year-old man dying suddenly of a heart attack; however, he was considered to have "decompensation or failure" and the autopsy revealed mitral insufficiency and chronic passive congestion of the liver. Steinitz[67, 68, 69] analyzed five infants, all of whom suffered from disease known to affect body composition seriously: his year-old "atrophischen und rachitischen Kind" was marasmic and the others, aged 2½ to 4 months, died of diarrhea. Widdowson and associates[76] have recently presented data on four subjects: a 4½-year-old boy dying of tuberculous meningitis, a 25-year-old man with uremia, a 48-year-old man with endocarditis, edema, and malnutrition, and a 42-year-old woman who committed suicide by drowning. The first three subjects can in no way be representative of the normal state of body composition, while the fourth, though free from disease, presented a rather marked deviation from normal body build (weight 94 pounds, height 66½ inches).

Sommerfeld[64] analyzed the bodies of two young infants, aged 4 weeks and 3 months, for water, nitrogen, fat, and ash. The first subject died of malnutrition and diarrhea, but the second was described as being well developed, although he "had been under treatment for enteritis and furunculosis" and weighed only 4,340 grams at the time of death. The immediate cause of death was not stated. Reports of analyses of four presumably normal adults for total body water are also available in the older German literature.[1, 4]

To my knowledge, the reports mentioned above represent the sum total of the attempts made during the past century to apply the method of direct

chemical analysis to the study of body composition in postnatal man, exclusive of the neonate.

The obvious limitations of the direct method have led to the development of indirect approaches to the determination of total body composition in postnatal man. Shohl[62] arrived at an estimate of the composition of the adult through calculations based on individual organ composition and organ weights relative to total body mass at different ages. Various groups of workers, notably Stearns[66] and Duckworth and Warnock,[15] have attacked the problem through a consideration of the results of metabolic balance studies on normal infants and children. Having assumed a given chemical composition for the newborn infant, cumulative retention should theoretically represent the actual increase in the particular constituent in question; total body composition can then be calculated for any given time within the balance period.

Several factors emerge to limit the usefulness of the balance method for this particular purpose. Unequivocal discrepancies have been found between observed and expected retentions in that the former usually exceed, and by a wide margin, what might be anticipated on the basis of growth. Customary balance procedure consists of measurement of total intake and of outgo in urine and feces. Excretion of minerals and nitrogen can also take place via skin, and nasal and conjunctival secretions; the magnitude of cutaneous excretion has been measured in both infants and adults and appears to be appreciable.[24, 49, 71] Swanson's study revealed that fully one-third of the calculated retention of potassium was lost through the skin of infants, the values for sodium being 9 to 13 per cent and for chloride 13 to 18 per cent. Calcium and phosphorus losses were considerably less, amounting to 1.4 to 4.6 mg. and 0.3 to 8.0 mg. daily, respectively. Gamble[26] has called attention to the fact that young infants do not normally exist in a state of perfect electrolyte equilibrium, but rather exhibit daily fluctuations in extracellular fluid volume. Moreover, he and his co-workers have pointed out that distortions in electrolyte composition brought on by introducing a "load" require several days for correction.[27] As Gamble puts it: "It is very disappointing that in spite of our present excellent techniques for measuring the intake of electrolytes in the food and their outgo in the urine and stools, we are unable to obtain precise definition of balance because of two obstacles which apply particularly to the extracellular electrolytes. One of them is the loss of electrolytes insensibly by way of the skin, which we have no practicable means of measuring directly. The other hindrance is an extensive oscillation of balance for water and electrolytes, which is apparently a normal feature of extracellular fluid regulation." And quoting a particular experimental situation, "The insensible loss produced in this instance a 300 per cent error in the measurement of retention by the orthodox method. This error is very much larger for the infant than for the adult, because of his relatively much larger surface area. Measurements of retention of sodium and chloride by growing children, recorded in the literature, are so large because of this error that if these measurements defined actual gain, the children would in the course of a few years

approach the fate of the emigrees from Sodom and Gomorrah."[26]

It is always necessary to assume that the subject is in equilibrium at the beginning of the balance period; if by chance he is either depleted or "supermineralized" by virtue of pre-existing deficiencies, disease, or improper feeding, he is no longer "normal" with regard to the particular balance situation. Since cutaneous losses must be covered by intake, metabolic balances do provide valuable information relative to diet planning and nutritional requirements.

Shohl[62] noted that there was a very poor correlation between gain in weight and retention of minerals, and commented on the balance method of approach as follows: "When one applies this method to a study of conditions during which accretion is taking place, such as growth of children and pregnancy, the problem becomes much more complicated. The difficulty is to determine what retentions are optimal. Neither maximal nor minimal retentions should be so regarded. There is no ideal standard. Results can be compared only with adequate data obtained under known conditions. Rational empiricism is our best guide."

Yet another approach has been used by some investigators. Calcium, for example, is found almost exclusively in skeletal tissue. A large portion of the body potassium is in muscle, while chloride is present for the most part in extracellular fluid. Knowing the relative proportions of skeletal tissue present at various ages together with the calcium content of bone and cartilage, one should be able to approximate total body calcium at various ages by suitable calculations. Although there is a great deal of information on visceral organ weights in infants and children, data concerning relative skeletal and muscle weights are few in number. A series of skeletal weights for infants and children of various ages are presented in The White House Conference Report[74] and are credited to Venar and Todd, with a note that the data are "unpublished." There is no way therefore of assessing the reliability of these data in terms of the body build and nutritional status of the subjects employed. The report also lists skeletal muscle weights for infants, children, and adults, and again no information is included as to the nutritional status of the subjects. In view of the paucity of data, the accuracy of this type of approach to total body composition in growing infants and children is open to question.

During the past few years the isotopic dilution method has been found to offer yet another indirect approach to the problem of total body composition. Either stable or radioactive isotopes can be used. The procedure consists of introducing a known amount of the material in question, appropriately labelled with its isotope, into the body, waiting for the isotope to come into equilibrium with its "brother" molecules, and then measuring the extent to which it has been diluted during the mixing process. The advantage of this method lies in the fact that living subjects can be employed and that repeated measurements can be made on the same subject. The actual amount of material injected is extremely small in comparison to that contained within the body, so that net metabolism is not measurably altered. Unfortunately, certain technical considerations, among them the possibility of radiation

TABLE I. CHEMICAL STRUCTURE OF NEWBORN INFANT AND ADULT

NO. SUBJECTS	AUTHOR		%			MEQ./KG.			GM./KG.			MG./KG.			ANALYTICAL METHOD
			H_2O	FAT	N	Na	Cl	K	Ca	P	Mg	Fe	Cu	Zn	
						*Newborn Infants**									
6	Camerer and Söldner[8]	Max.	73.0	16.1	2.18	80.7	52.5	43.1	9.28	5.30	0.225	150	--	--	Carcass analysis
		Min.	69.2	10.2	1.79	66.9	42.7	36.5	4.99	3.43	0.101	108	--	--	
		Av.	71.8	12.2	1.97	73.7	49.7	40.4	7.24	4.47	0.168	129	--	--	
6	Widdowson[75]	Av.	69.1	16.1	1.90	82.5	--	44.1	8.01	4.68	0.218	78.8	3.95	16.1	Carcass analysis
						Adult									
1	Mitchell et al.[49]		67.85	12.5	2.31	--	--	--	15.96	7.71	--	--	--	--	Carcass analysis
1	Widdowson[76] (Subject "L")		56.0	23.6	2.30	73.7	--	55.5	18.95	9.86	0.326	45.9	1.37	16.8	Carcass analysis
4	Older German literature[1, 4]		64.4 Range (59.0-67.6)	--	--	--	--	--	--	--	--	--	--	--	Carcass analysis
	Shohl[62]		59	18	3.0	39	34	56	16	9.5	0.30	--	--	--	Calculated
						Males									
17 (H_2O)	Corsa et al.[13]	Max.	70.2	--	--	54.1	35.2	57.1							Isotopic dilution
25 (Na)	Forbes & Perley[23]	Min.	55.9	--	--	32.3	27.9	37.0							
29 (K)	Dunning et al.[16]	Av.	61.8	--	--	41.9	31.6	46.3							
26 (Cl)	Schloerb et al.[60]														
						Females									
11 (H_2O)		Max.	59.9	--	--	41.6	29.3	--							Isotopic dilution
7 (Na)		Min.	45.6	--	--	36.8	25.8	--							
26 (Cl)		Av.	51.9	--	--	39.5	28.6	--							

*A number of single analyses for newborn infants are reported in the literature (for references see[22]).

damage, serve to limit the general applicability of this method.

The usefulness of the isotopic dilution method depends on the demonstration of attainment of true equilibrium. In the case of total body water, equilibration curves indicate that complete mixing occurs within a relatively brief period, while radioactive sodium, chloride, and potassium equilibrate much more slowly. Until further proof is forthcoming, workers in this field have preferred to qualify the measured quantities by the adjective "exchangeable." Despite the lack of data on the precise relationship of the quantities measured by this method to the total amount of actual material in the body, the isotopic measurements do serve to indicate that portion of the total body content which is readily exchangeable and therefore metabolically active.

Before turning to a detailed consideration of the various aspects of chemical growth, the over-all picture of the contrast between the newborn infant and the adult will be presented (Table I). On a per kilogram basis the normal newborn infant contains about twice as much sodium, iron, and magnesium, three times as much copper, and one-half the amount of calcium and phosphorus as the adult. The adult contains somewhat more potassium and nitrogen and considerably less water than the infant; chloride content is 60 per cent of that of the infant. Sommerfeld's[64] 3-month-old subject contained 70.15 per cent water, 2.27 per cent nitrogen, 13.11 per cent fat, and 2.73 per cent ash; the values for water and nitrogen lie between those listed for the newborn infant and adult (Table I). Many workers have pointed out the desirability of expressing chemical composition in terms of fat-free body weight, since depot fat constitutes a "foreign body" so far as water and minerals are concerned. Moulton,[51] amplifying the results of the older German workers, emphasized that the composition of the fat-free portion of the body varies relatively little among adult subjects of various species. Spray and Widdowson[65] have recently reiterated this concept. It is now customary procedure for workers in the field of electrolyte physiology to refer analytical values to a basis of fat-free tissue. The specific gravity method of ascertaining the amount of fat in the living adult has been used with some success,[3, 50] but it would seem that there are many difficulties to be faced in applying it to infants and children. If fat were the only variable involved and other tissues remained constant in proportion to total body mass, specific gravity measurements could be readily translated into terms of per cent body fat. However applicable this assumption may be in the adult, lack of precise knowledge on relative skeletal and muscle weights in the infant and child would seem to preclude the use of this method. None of the brain lipids are in the form of neutral fat. The values set out in Table I were therefore related to total body weight (for calculations based on fat-free body weight, see Shohl[62]).

Lest one gain the impression that body composition for subjects of a given age is constant, the range of variability has been included in Table I. Since only subjects who are supposedly normal are included, the range is sufficiently great to make one hesitate to accept results obtained on a single subject as representative of a particular age group.

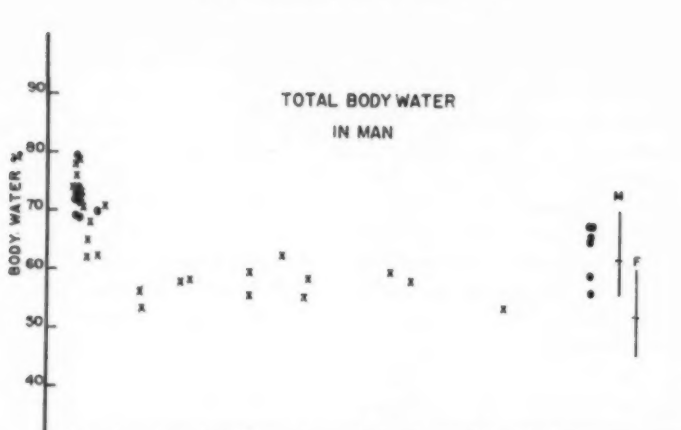

Fig. 1.—Total body water at various ages, in terms of per cent body weight. •—Carcass analysis; x—isotopic dilution. *M*, Males; *F*, females, by isotopic dilution. Data of Table I and references[22, 23, 64].

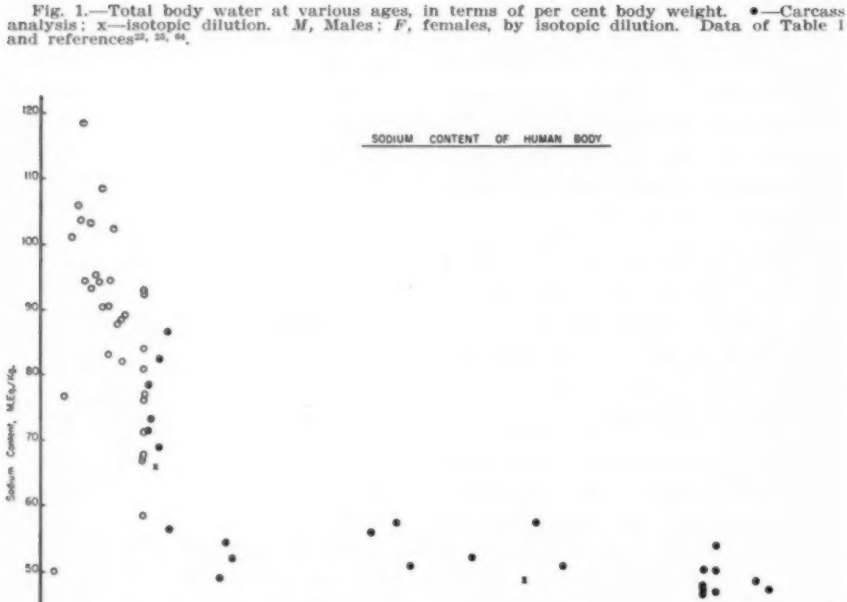

Fig. 2.—Changes in total body sodium during growth. ○—Carcass analysis; •—males, x—females, by isotopic dilution. (Reproduced from Forbes and Perley: J. Clin. Investigation **30**: 566, 1951.)

Granted that there are differences in composition between the newborn infant and adult, the question still remains as to the manner in which these alterations are brought about: Does body composition change in some regular fashion as growth proceeds? Do the changes occur in such a manner that external dimensions give some clue to internal composition at any given age? Is the rate of change in body composition solely a function of age, or is some physical parameter, such as mass, intimately involved?

The various aspects of total body composition will now be taken up in some detail.

Total Body Water.—More information is available on this aspect of body composition than for any other single constituent. Carcass desiccation was first carried out a century ago, and von Hevesey and Hafer[31] used deuterium for this purpose in adults almost twenty years ago. More recently a series of determinations utilizing both antipyrine and deuterium were made on infants and children.[25] The diagram in Fig. 1 depicts changes in total body water content from the late fetal period to maturity. The human body becomes progressively drier during the period of infancy, with little if any change thereafter. Attempts have been made to express total water on a fat-free basis in the adult, since fatty tissue contains almost no water, but the literature contains no reference to similar attempts in children. Differences in fat content may well be responsible for the "dip" in the curve at 9 months of age and for the fact that adult males have a higher percentage of water than females.

Total Body Sodium.—Sodium content follows the same general course as water, exhibiting a sharp decline in infancy followed by a more gradual fall in later childhood. Most of the data set forth in Fig. 2 were compiled by the isotopic dilution method.[23] Widdowson's subject represents the only departure from the general trend (see Table I). That the decline in sodium content is not solely the result of the process of "drying out" of the body during growth is evident from the fact that water content diminishes more slowly than sodium. Much of the sodium is in the extracellular fluid compartment, and this compartment becomes smaller with advancing age.[20, 56] Just as in the case of body water, changes in body content of sodium are more profound in the infant and young child.

On a percentage basis, growth is also more rapid in infancy than for any other period of postnatal life: a change in weight from 3.3 to 10 kilograms occupies only one year of time, while the same percentage change, namely, 10 to 30 kilograms, requires an additional seven years for completion.* Both sodium and water content, on a per kilogram basis, are seen to decline most rapidly in infancy, and being in accord with the general plan of the growth process are undoubtedly an integral part of it. In addition to extracellular fluid, some sodium is found in the intracellular fluid of muscle, and

*The fundamental nature of the growth process cannot be grasped without the concept of percentage growth, in which change is related to the mass of tissue available for change. Considered solely from the viewpoint of gain, a change from 3.3 to 10 kilograms involves an increment of 6.7 kilograms per year, while during the second period, 10 to 30 kilograms, the average velocity is 2.8 kilograms per year. In terms of percentage gain, the difference in velocity becomes much more marked: during the first year of life, body weight increases by 200 per cent while for the next seven years, the average increase is only 28 per cent per year. Absolute growth is small during early infancy, yet relative or percentage growth is huge in comparison to later years. For a more complete discussion, see Wetzel.[12]

about 30 per cent of the total body sodium is in bone.[62]

Total Body Potassium.—Many analyses have been made of the bodies of fetuses and newborn infants for potassium. A large series of determinations on young male adults has recently been carried out by the isotopic dilution method. In contrast to sodium and water, the adult contains somewhat more potassium than does the infant, the values being 46 and 42 meq. per kilogram, respectively. The positive change during growth is much less than the negative change in sodium, so that the sum of these two cations undergoes a net decrease as growth proceeds. Except for the subjects studied by Steinitz and Widdowson, noted at the beginning of this section, there is no information available on total body potassium in infants and children. The existing data on total muscle mass in the infant and adult would indicate that this tissue comprises 32 to 44 per cent of the total weight of the adult in contrast to the newborn value of 20 to 24 per cent.[4, 38, 49] A large portion of the total body potassium of the adult is in muscle tissue; the fact that total body potassium increases only slightly during growth whereas there is a large relative increase in muscle mass would seem to indicate that a much larger share of the total body potassium is elsewhere than in muscle in the newborn infant.

Total Body Chloride.—Data for newborn infants have been presented above (Table I) together with estimates for young adults obtained by the bromide dilution method. There are no published figures for carcass analysis in adults, presumably because of the special analytical problems involved. Burch and his co-workers are now investigating the isotopic dilution method in adults, but have not as yet published results on normal subjects. The adult body contains less chloride than the infant, on a per kilogram basis, but no accurate data exist on total body chloride content for children. In view of the differences in major sites of deposition of sodium and chloride within the body—sodium in bone, chloride in skin—it is of interest that the total body Na/Cl ratio changes relatively little with age and tends to approximate that of the blood serum.

In a recent paper,[22] attention was called to the possibility that certain inferences might be made through interpolations of existing data. Observational data on fetuses and newborn infants, plotted logarithmically, could be extrapolated to include data obtained on young adults.

It is necessary at this point to make a digression in an attempt to explain the method employed in arriving at these results. The method involves the use of the principle of relative or differential growth, first emphasized by Huxley.[35] In practice, one applies this method by plotting the logarithm of the total amount of the body constituent in question against the logarithm of some parameter of the body totality, for example, weight. When this is done for sodium and water, a straight line relationship is seen to hold over a rather wide range of body weights, with close agreement between values obtained by carcass analysis and by isotopic dilution.[22, 23] Chemical growth, at least with regard to sodium and water, appears to be regular and systematic when viewed in this manner: increases in body weight are accompanied by predictable changes in these

constituents. It is conceivable that the scatter about the calculated regression lines could be somewhat reduced by plotting fat-free rather than total body weight on the abscissae. Iob and Swanson[36] used fat-free body weight in carrying out calculations of this general sort for chemical growth in the fetus.

This hypothesis has been extended to include total body potassium as well.[22] Double logarithmic plots of total body potassium against body weight resulted in a linear relationship for the late fetal period. Moreover, extrapolation of the calculated line was found to include neatly data obtained on adults by the isotopic dilution method. If one assumes that potassium accretion, systematic during late fetal life, continues in like fashion in infancy and childhood, it becomes possible to calculate total body potassium for normal subjects of known body weight.

I have recently completed similar calculations for total body chloride. Just as in the case of potassium, the regression line for chloride, calculated from fetal analyses, can be extrapolated to include that for adults obtained by the bromide dilution method. If the analogy with sodium and water can be justified, potassium and chloride accretion also occur in a systematic fashion during postnatal growth, when viewed logarithmically. Prediction equations for water, sodium, potassium, and chloride are given in Table II to follow, along with calculated values for certain selected body weights. In the interest of convenience, the equations and predicted values are given as c.c. or meq. per kilogram rather than in terms of total body content.*

The general course of postnatal chemical growth in terms of H_2O, Na, K, and Cl is depicted in Fig. 3. Here, total body content on a per kilogram basis is plotted against body weight on a double logarithmic grid. The rather sharp decline in Na and Cl content, the more gradual fall in per cent water, and the very slow rise of potassium are easily visualized here. The regularity of the chemical growth process is now apparent, in sharp contrast to the curvilinear relationships noted when rectangular coordinates are employed (Figs. 1 and 2). It should be remembered that the equations listed in Table II are applicable only to the period of life extending from the latter half of gestation to the young adult. It has been demonstrated that they do not hold for the early fetal period,[22] and data are not yet available to indicate whether or not significant changes in total body composition, at least for the four elements in question, occur with the onset of senility. Information on postnatal chemical growth for other

TABLE II. REGRESSION EQUATIONS AND PREDICTED VALUES FOR TOTAL BODY WATER, SODIUM, CHLORIDE, AND POTASSIUM

BODY WEIGHT (KG.)	1	3.3	10	30	70	EQUATION*
H_2O (%)	80.6	72.6	65.9	60.0	55.7	$\log y/kg. = -0.087\ x + 3.167$
Na (meq./kg.)	91.0	74.5	61.8	51.4	44.6	$\log y/kg. = -0.168\ x + 2.463$
Cl (meq./kg.)	63.1	50.7	40.6	32.9	27.9	$\log y/kg. = -0.192\ x + 2.376$
K (meq./kg.)	40.6	41.7	42.7	43.7	44.7	$\log y/kg. = +0.022\ x + 1.543$

*y stands for the body constituent in question, c.c. or meq., and x for body weight in grams.

*In terms of total body content, the equation for chloride is: log Cl, meq. = 0.808 log body wgt., gm.—0.624. The standard deviation from regression is 0.047, and the correlation coefficient 0.986. For similar computations with regard to H_2O, Na and K, see reference[22].

body constituents is not yet available in sufficient quantity to permit similar calculations.

Aside from the fact that the straight line relationships noted above are descriptive, the concept of differential, or relative, growth is implied. *Specific growth rate* is defined as the rate of change of body mass per unit mass, dw/w dt (gm./gm./day), in contrast to simple growth rate, which is merely the rate of change in mass, dw/dt (gm./day). Now dw/w dt is the equivalent of d(log w)/dt, so that specific growth rate can be thought of in terms of the rate of change of the logarithm of mass (log gm./day). The linear relationships illustrated above are of the general form log y = b + k · log x (analogous to the arithmetic equation for a straight line y = b + kx) in which *k* is the slope of the line and *b* the intercept on the y-axis. Differentiating, we have d(log y)/dt = k · d(log x)/ dt, whence it follows that *k*, in addition to being the slope, is a proportionality constant indicating the ratio between two specific growth rates; it is therefore referred to as the differential growth ratio. In terms of percentage growth, regardless of initial weight, for each per cent change in body mass, sodium increases by 0.83 per cent, water by 0.91 per cent, chloride by 0.81 per cent, and potassium by 1.02 per cent. These constituents therefore behave as if they possess specific growth rates of their own.

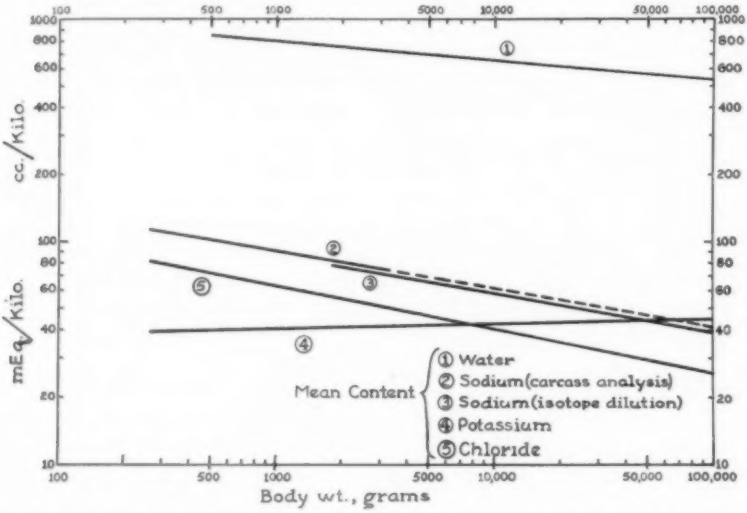

Fig. 3.—Double logarithmic plots of total body water, sodium, potassium, and chloride against body weight. (Modified from Forbes: Pediatrics 9: 58, 1952.)

This concept of chemical growth implies that body composition is continuously changing as growth proceeds, and provides the only means at hand for calculating retentions due to normal growth.[22]

The rapidity with which body composition changes in infancy in contrast to later childhood now becomes more understandable. As noted above (see footnote, p. 209) both *specific* growth rate and simple growth rate are

high in infancy; the rate at which body mass is changing is more rapid at that time than at any other time during the growth period. Admittedly, chemical growth is the result of interplay of multiple factors and the logarithmic equations presented above undoubtedly represent only a first approximation to an accurate portrayal of this aspect of the general growth process. However, this concept does emphasize the value of characterizing growth in logarithmic terms, for in so doing it is revealed as a process involving multiplication. Since infancy is a period of rapid multiplication of tissue, changes in body composition might be expected to take place quickly during that phase of growth.

Hamilton[29] employed the differential growth principle some years ago in arriving at an estimate for total body water in the adult. Iob and Swanson[36] have calculated differential growth ratios for a number of chemical constituents in the human fetus. Needham[53] lists ratios for a large number of constituents in a variety of species and points out that many of the k values show relatively little interspecies variation. The similarities in k values were so striking that he speaks of the "fundamental chemical ground-plan of animal growth." Vertebrate protoplasm retains its fundamental identity regardless of species.

Total Body Calcium.—On a per kilogram basis the adult body contains approximately twice as much calcium as the newborn infant. Many fetuses have been analyzed for this element, but no analyses have been carried out on normal infants and children. Because of the possibility of significant radiation damage (radioactive calcium possesses a long half-life and would of course localize in bone), the isotopic dilution method holds little promise of providing a ready means of measuring total body calcium. A large number of balance studies have been carried out on growing infants and children; emphasis has usually been placed on nutritional phases with particular reference to dietary requirements for normal growth and development. Duckworth and Warnock[15] and Holmes[33] have recently reviewed the efforts made to translate balance data into total body content and have added certain data on their own. Fig. 4 is taken from Duckworth and Warnock's report and illustrates the results of several types of approach. For Curve "DW" total body calcium was assumed to be 125 grams at 2 years of age, subsequent content being calculated according to balance data from the literature; only those balance periods in which intakes were 500 mg. or more daily were used in making the calculations. The curve represents both sexes until 10 years; thereafter it applies only to females. Curve "M" was drawn in accordance with the results of Mitchell's calculations[48] and applies only to females: per cent body content of calcium was assumed to progress steadily from 0.8 per cent at birth to 1.55 per cent at maturity, gains in calcium during growth being figured as 0.8 per cent of each gain in body weight in the first month of life with gradual progression to 2.30 per cent at maturity (thus yielding an average value of 1.55 per cent). Curve "S" is based on Shohl's data in which changes in proportionate skeletal weight and per cent calcium in bone, and an adult value of 1.65 per cent calcium were assumed and taken into account. Curve "SL" represents calculations based on Sherman

and Lanford's collected data[61] on calcium retentions in growing children. Curve "VT" is based on Venar and Todd's data on skeletal weights in girls.[74] From the curve for skeletal growth, total body calcium was calculated on the assumption that the skeleton contains 21.4 per cent calcium. The results by Curve "DW" indicate a lower total body content presumably because the data were restricted to subjects who were not deficient in this mineral, and therefore not repairing an existing deficit at the time of the study.

Holmes[33] presents two other possible solutions to this problem. Using Venar and Todd's data, the following calculations were made (Method C): gains in calcium were assumed to progress steadily from 6.8 per cent of skeletal weight gain at birth to 33.5 per cent at maturity, thus providing an average value of 20.2 per cent. Method D is as follows: "On the assumption that the pattern of calcification found in the

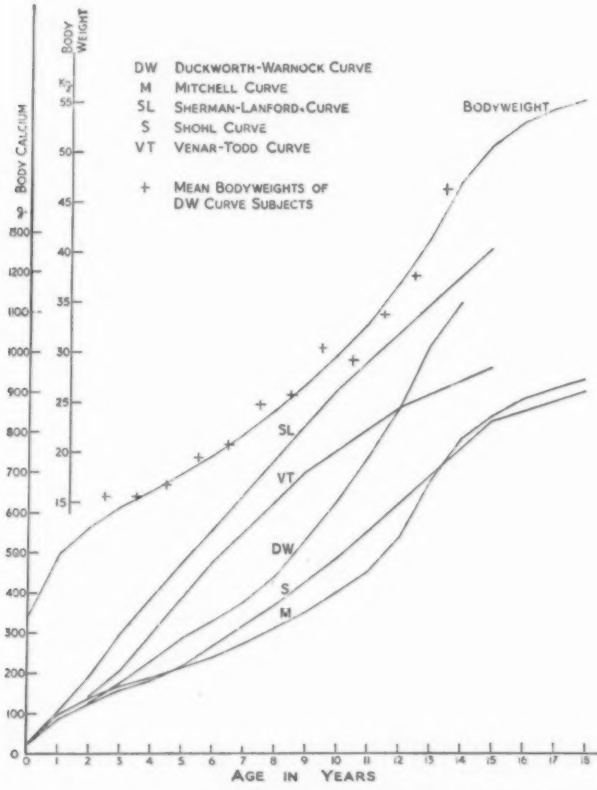

Fig. 4.—Calculated total body calcium during growth. The calcium content of the body at different ages according to several authors, together with Mitchell's growth curve for girls and the mean body weights of subjects (mostly girls) cited by Duckworth and Warnock. For explanation of symbols and curves, see text. (Reproduced from Duckworth and Warnock: Nutrition Abstr. & Rev. 12: 167, 1942.)

rat applies also to man and that in man receiving adequate calcium, the percentage increments in calcium are almost identical with those for body weight, the increment of calcium in man was computed from the weight curve representing the total increment in calcium (1,091 grams), i.e., the difference in the calcium content of the adult (70 kilograms times 1.6 per cent calcium) and that of the newborn (3.6 kilograms times 0.8 per cent)."

calcium metabolism for many years. Fig. 5 is taken from Stearns' review.[66] Values for fetal content were drawn from the literature on carcass analysis while those for postnatal life were based on balance determinations together with empirically observed weight gains. These curves indicate that calcium growth lags behind body growth to the extent that the infant cannot possibly fail to show an actual decrease in per cent calcium content

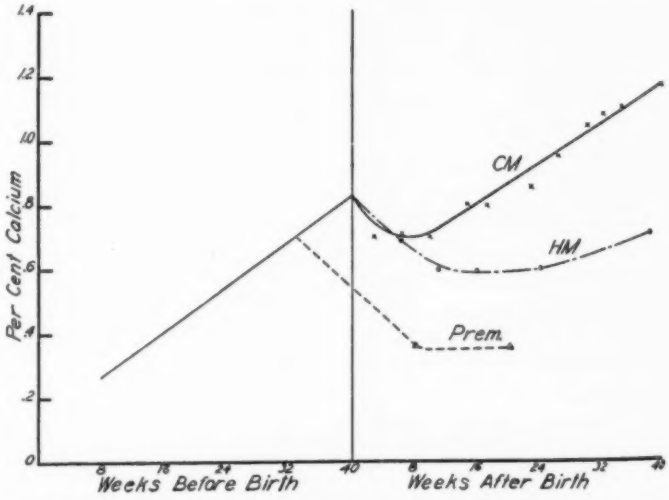

Fig. 5.—Changes in relative calcium content of the fetus and infant. The regression line of calcium content of fetus is drawn from data in the literature. *CM*, Infants fed cow's milk; *HM*, infants fed human milk; *Prem.*, prematurely born infants fed human milk. (Reproduced from Stearns: Physiol. Rev. **19**: 416, 1939.)

Mitchell and associates discuss calcium growth in a recent article.[49] On theoretical grounds they have constructed a quartic equation* from which calcium increments and total body content can be calculated for any given age.

Stearns, Jeans, and their associates at the University of Iowa have studied during the first few months of life. This decrease is more marked in the breast-fed infant than for the one fed cow's milk (due to higher calcium intakes and retentions for the latter) and is quite striking in the premature infant. "The marked difference between the calcium retentions of infants given high calcium feedings plus vitamin D and those fed human milk has aroused much discussion as to the question of 'super-mineralization,' of the infant

*$W = 28 + 86.828\ t - 16.5105\ t^2 + 1.5625\ t^3 - 0.04114\ t^4$, where W represents total body calcium in grams and t is in years. The formula applies only to males.

fed cow's milk. . . . The curves for percentage of body calcium in infants given human and cow's milk are so dissimilar that either one must assume marked differences in relative proportion of skeletal to body weight (or in amount of fat deposits) or a very wide range of 'normal' calcification of bone. The changes in percentage of calcium would necessitate an average decrease in the breast-fed infant of at least 5 per cent in the relative proportion of body weight due to skeleton if calcium content were even maintained constant. Anatomical data, however, show that the wet weight of the skeleton remains practically a constant proportion of body weight during infancy. For the differences to be attributable to differences in fat content, nearly 70 per cent of the weight gain of the breast-fed infant would be due to fat. A true decrease in calcium content of bone must be assumed. Eliot and Park state that 'the long bones of the extremities of the healthy fetus at term are almost completely filled with cancellous bone. The marrow cavity does not become well developed until sometime after birth. The meaning of this must be that under normal conditions the fetus is born with a store of calcium in the skeleton.' Hamilton has construed this observation to mean that the relative depletion of body calcium in early infancy is normal and is a utilization of excess stores."[66] In evaluating Stearns' conclusions, note should be taken of the fact that the breast-fed infants portrayed in Fig. 5 received no vitamin D whereas those fed cow's milk were supplied with ample supplements of this vitamin.

The various assumptions made in constructing the curves for calcium growth are discussed at length in Duckworth and Warnock's[15] and Holmes'[33] papers. It is unfortunate that the existing data relative to skeletal growth in infancy and childhood are open to some criticism, for 99 per cent of the total body calcium is in bone,* so that accurate knowledge of skeletal weight should make for easy calculation of total body calcium. The difficulties involved in calculating body composition from balance determinations were discussed in an earlier section of this report. Many investigators have noted that the degree of positive retention has a great deal to do with intake. According to Stearns,[66] "studies of the relation between calcium intake and retention indicate that a direct relation exists between the two at all levels of milk intake studied, and offer

TABLE III. TOTAL BODY CALCIUM AT TWO SELECTED AGES*

40 WEEKS		10 YEARS OLD	
METHOD	TOTAL CA. (GM.)	METHOD	TOTAL CA. (GM.)
Holmes "C"	56	Mitchell	396
Stearns (human milk)	63+	Duckworth "M"	400
Stearns (cow's milk)	105+	Duckworth "S"	480
Holmes "D"	130	Holmes "D"	542
		Holmes "C"	583
		Duckworth "DW"	620
		Duckworth "VT"	750
		Duckworth "SL"	900

*Calculated from the literature. For explanation see text.
+ Body weight assumed to be 9 kilos.

*This figure applies to both infant[28] and adult.[69]

no evidence that the maximum possible retention has been attained at any given age during infancy." Either the body tends to store the excess calcium retained at high levels of intake or the distortion in body composition produced thereby is corrected so slowly that prolonged balance periods would be necessary for its detection. Let us take as an example a 10-year-old child and an infant of 40 weeks for calculation of total body calcium according to the various methods noted above (Table III). This is an astounding range of values. Evidently any of the methods for approximating total body calcium during growth require assumptions of such nature as to leave the reader with the distinct impression that an accurate answer to the question has not yet been found.

TABLE IV. TOTAL BODY MAGNESIUM AT VARIOUS AGES

AGE*	SKELETAL MAGNESIUM (GM.)	SOFT TISSUE MAGNESIUM (GM.)	TOTAL BODY MAGNESIUM (GM.)
Birth	0.46	0.26	0.73
0-1†	0.93	0.52	1.45
1-2†	1.85	1.06	2.91
2-3	2.78	1.60	4.38
3-4	3.74	1.81	5.55
4-5	4.76	2.00	6.76
5-6	5.74	2.21	7.95
6-7	6.57	2.45	9.02
7-8	7.59	2.72	10.31
8-9	9.06	3.01	12.07
9-10	10.80	3.33	14.13
10-11	12.67	3.69	16.36
11-12	14.80	4.09	18.89
12-13	17.39	4.58	21.97
13-14	19.83	5.20	25.03

*Calculations for center point of each interval.

†Interpolated because of inadequacy of skeletal calcium values.

Total Body Magnesium.—Duckworth and Warnock[15] have summarized the available data on this aspect of chemical growth. Calculated values for total body magnesium are set forth in Table IV. Since the magnesium content of the skeleton is relatively constant throughout life, they calculated total body content on the basis of skeletal weight, and the assumption that soft tissue magnesium, estimated for the adult at 0.0117 per cent, remained constant throughout growth. Shohl[62] and Widdowson and co-workers[76] give values for total body magnesium in the adult of 21 and 14.7 grams, respectively. The differences between total body content calculated in this way and by the balance method are quite striking in the case of magnesium, Duckworth and Warnock's figures indicating that total body magnesium would amount to well over 150 grams in the young adult on the basis of observed retentions.

Total Body Phosphorus.—The adult body contains approximately twice as much phosphorus, on a percentage basis, as the newborn infant. The increase in phosphorus content lags slightly behind the increase in calcium content, the Ca/P ratios being approximately 1.96 and 1.66, respectively, for adult and infant. Although calculations of total body phosphorus during infancy and childhood might conceivably be approached in the same manner as calcium, apparently no attempts to do this are recorded in the literature. Macy conducted studies of phosphorus balance in a number of children,[44] and others have studied infants of varying ages. Gross inspection of the balance data brings one to the obvious conclusion that retentions, just as in the case of calcium, are far in excess of expected growth requirements. Calculations of total body phosphorus on the basis of expected skeletal weight is scarcely feasible in view of the fact that about 20 per cent of the total body phosphorus of the infant[38] and adult[62] is in extraskeletal

tissues. It has been known for some time that dietary Ca/P ratios are of considerable importance for the newborn infant since a diet high in phosphorus is occasionally responsible for the development of neonatal tetany. Certainly at this time of life excessive phosphorus retentions are undesirable.

Total Body Nitrogen.—Nitrogen content on a percentage basis increases slowly as growth proceeds but not to the extent shown by calcium and phosphorus. Total body nitrogen in Sommerfeld's[64] 4-month-old subject (2.27 per cent) was found to be somewhat closer to the adult value than that for the newborn infant. Stearns'[66] calculations are illustrated in Fig. 6 and reveal the same differences between infants fed cow's milk and human milk as in the case of calcium. The undiluted cow's milk formula employed has of course a much higher protein content than breast milk. "Changes in both nitrogen and calcium composition of the body are thus very similar for the same dietary regimes. . . . With phosphorus and nitrogen as with calcium, the quantity retained by the infant is directly proportional to the intake, if the food is in a form well utilized by the infant."[66]

Total Body Iron, Copper, and Zinc.—Differences between the infant and adult are given in Table I, from which it is to be noted that the newborn infant contains considerably more iron and copper than the adult, but about the same amount of zinc. The only information available on total body con-

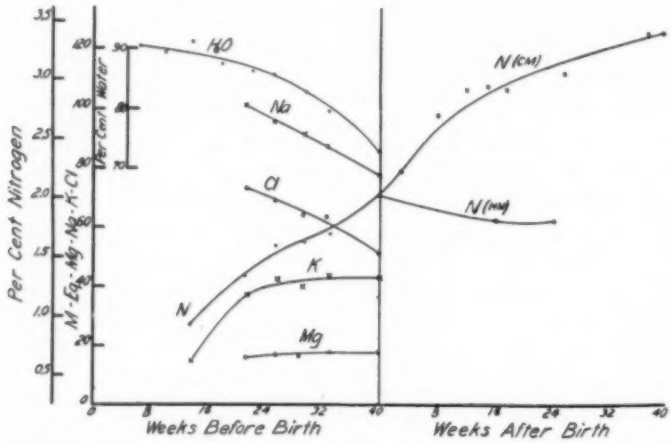

Fig. 6.—Changes in nitrogen, water, and electrolyte content of the fetus, and in nitrogen content of the infant. *CM* and *HM*, Infants fed cow's and human milk, respectively. (Reproduced from Stearns: Physiol. Rev. 19: 422, 1939.)

tent of these elements during childhood is the single analysis performed by Widdowson and collaborators[76] on a 4½-year-old boy dying of tuberculous meningitis. In this subject iron and zinc content were approximately the same as the adult whereas copper content was midway between the infant and adult values. Single organs have been analyzed for their content of these three elements, however, and reference will be made to these studies later.

Total Body Fat.—In contrast to many mammals, in which the neonate

contains only 1 or 2 per cent fat and the acquisition of a normal amount of adult fat is a gradual process during postnatal growth, total body fat is about the same in the human newborn and adult. The human organism acquires its body fat during the latter third of intrauterine life and is in this one respect more "mature" than many mammals at birth. With the one exception of Sommerfeld's subject, no direct analyses for total body fat are available for postnatal infants and children, and the experiments designed to measure this body constituent by specific gravity determinations in the adult do not seem to have been applied to younger subjects. Stuart and Sobel[70] have carried out roentgenographic studies of the extremities of infants and children, in which measurements of the thickness of the shadow cast by the subcutaneous tissues were made. By this method they showed that the amount of subcutaneous tissue, most of which is fat, varies considerably during growth. There is a rapid increase in thickness after birth to a maximum at approximately 9 months of age, with a subsequent gradual fall to a minimum value (approximately one-half that of the value at 9 months) at 5 years of age. The thickness of the subcutaneous tissue layer then remains about the same until shortly before puberty when there is again an increase. Infant depot fat differs in certain physical properties from that of the adult: the melting point is higher and the iodine number lower than for adult fat, and the relative proportion of oleic acid and some of the short chain fatty acids is far greater.[46] Attempts have been made to relate these distinctive properties to the occurrence of sclerema neonatorum.[34]

ORGAN ANALYSES

Skin.—This organ serves the unique function of acting as a storehouse for chloride. With the exception of certain specialized tissues, such as red blood cells, gastric mucosa, pancreas, uterus, and testes, most organs and tissues contain considerably more sodium than chloride on an equivalent basis. In the adult, the skin Na/Cl ratio is of the order of 0.8-1.2/1[17, 62] in contrast to 1.4/1 for blood serum, 1.8/1 for muscle and 3-4/1 for bone. High Na/Cl ratios are found in infant skin, however[39]; but since the skin of the infant makes up a considerably greater portion of total body weight than in the adult, it still constitutes a sizeable reservoir for chloride. According to Shohl's calculations the adult skin and subcutaneous tissues contain one-third of the total body chloride while these tissues comprise but 26 per cent of the total body weight. In Klose's[38] newborn subject, the skin comprised 15.8 per cent and the subcutaneous fat 14.5 per cent of the total body weight (the latter being electrolyte-free) while containing 26 per cent of the total body chloride. Kerpel-Fronius[37] has calculated that the skin of the newborn infant contains 15 per cent of the total body extracellular fluid, while the adult figure stands at 8 per cent.

Brown[5] studied a large series of samples of human skin obtained at autopsy, in which the ages of the subjects ranged from the 5-month fetus to the 78-year-old adult. Since fat content varies widely, it is unfortunate that values were expressed in terms of original skin. Fig. 7 is taken from his paper to show the variation in total ash, calcium, magnesium, and silicon content with age. The values are at a maximum at about the time of birth, following which there is a sharp fall in

calcium, magnesium, and total ash to a minimum at approximately 10 years of age; later there is a gradual increase in concentration. Silicon does not follow this general course, but shows a gradual decline with increasing age. Shohl states that the decrease in silicon content parallels the loss of elasticity of the skin as age proceeds. Sodium, potassium, phosphorus, and water content all exhibited marked variability whether a true electrolyte "growth curve" exists for human skin.

Bone.—The chemical structure of mammalian bone has been the subject of intensive investigation for many years. Despite this emphasis on bone composition there have been few systematic studies on age variation. Age changes in the rat skeleton have been worked out by Hammett in some detail.[30] As growth proceeds, there is a

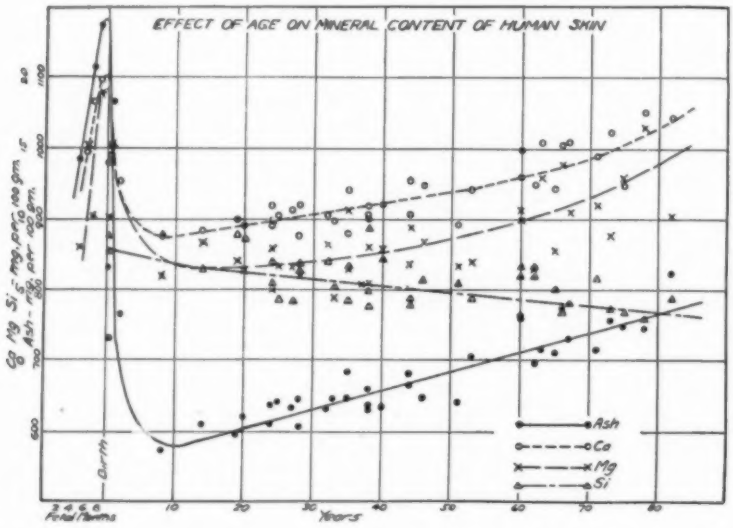

Fig. 7.—Changes in mineral content of skin with age. (Reproduced from Brown: J. Biol. Chem. 75: 789, 1927.)

but no consistent age trend; chloride analyses were not done.

There are a few reports available concerning the composition of skin on a fat-free basis.[17, 39] These show a decreasing water and an increasing nitrogen content with growth. Cholesterol content, on a dry weight basis, falls with age.[7]

Eisele and Eichelberger's[17] recent series of analyses of adult skin samples should stimulate efforts, utilizing modern analytical techniques, to discover decline in water content balanced by an increase in total ash, while total organic matter increases slightly. Calcium and phosphorus increments parallel those for total ash. Plots of percentage increments reveal that sex differences in chemical bone growth make their appearance well before puberty. The rate at which calcium and phosphorus are deposited in rat bone varies with age, the point of maximal deposition occurring at 50 days of age in the male and at 30 days in the female.

Percentage increments in magnesium tend to lag behind those for calcium and phosphorus at the time of puberty.

Surveys of the literature on bone composition are made difficult by virtue of the fact that values are not presented in a consistent manner. Often the author fails to indicate whether or not the marrow was included in the analytical specimen. Some results are expressed in terms of fresh tissue, others as dry weight or dry fat-free weight, and still others in terms of per cent bone ash. Since Mitchell and associates[49] have shown that there is considerable variability within the various components of a given skeleton, serial studies of skeletal "chemical growth" should utilize a consistent site for the taking of specimens for analysis in all subjects.

For certain minerals the skeleton is literally a storehouse. In the adult, 99 per cent of the total body calcium is to be found there, along with 80 per cent of the phosphorus, 50 per cent of the magnesium, and 30 per cent of the sodium. For the infant these values are 98.6, 80, 70, and 32 per cent, respectively.[38] The skeleton provides rigidity and architecture to the organism. But more and more evidence is accumulating to indicate that skeletal minerals possess a degree of lability and metabolic activity to the extent that this organ may also serve the purpose of providing a reserve supply of minerals with which the demands of stressful situations can be met. Isotopic studies have revealed appreciable turnover rates for certain skeletal components. Skeletal magnesium may be rapidly depleted in response to certain metabolic demands.

Follis[21] has recently reviewed the literature bearing on age changes in the calcium, phosphorus, and carbonate content of the human rib, and has added data of his own. When expressed on a dry fat-free basis, the calcium content does not change appreciably with age, averaging 23.3 and 25.7 per cent with and without the marrow elements, respectively. Phosphorus averages 11.7 per cent and shows a very slight tendency to decline with increasing age. Carbonate content undergoes a definite age change, rising from 2.38 per cent in the fetus to 3.37 per cent in the adult.

Hodges and co-workers[32] have reported a large series of analyses for strontium content of human bone in which the age of the subjects ranged from the fetus to 75 years. The fetal specimens contained an average of 0.016 per cent strontium (in per cent of bone ash) and the others 0.024 per cent with no observable age variation during postnatal life. This element probably has no metabolic function aside from its toxic effect in inhibiting bone calcification[63] but being in group IIA of the Periodic Table tends to follow calcium in its distribution within the body.

Duckworth and Warnock[15] have summarized the existing data on magnesium content and conclude that the values do not change greatly during growth. For the young fetus magnesium values fall within the rather narrow range of 0.7 to 0.9 per cent of total bone ash, while those for the term fetus and newborn infant show a fairly wide variation (0.5 to 1.2 per cent), with an average of approximately 0.7 per cent as estimated from the graph in Duckworth and Warnock's article. Children and adults through the age of 60 years are also represented, and although there is con-

siderable scattering of the values (0.4 to 0.9 per cent) the average value is seen to remain rather constant at about 0.7 per cent throughout the postnatal years.

Since it has been shown that the various portions of the skeleton may exhibit differences in chemical composition, it is of interest to compare the composition of the entire skeleton of the infant with that of the adult. Table V lists the available data. The changes are in accord with those noted for other tissues: growth involves a decrease in water content, and an increase in nitrogen and ash. Bürger and Schlomka[7] also noted an increase in nitrogen content of human bone with age.

TABLE V. COMPOSITION OF ENTIRE SKELETON

AUTHOR	AGE	% BODY WEIGHT	% FAT	PER CENT FAT-FREE TISSUE								
				H_2O	N	ASH	Na	K	Cl	Ca	P	Mg
Klose[38]	Newborn	15.99	2.6	64.0	2.77	15.02	0.322	0.156	0.124	5.12	3.14	0.139
Swanson and Iob[72]	Newborn	9.7	1.07	56.6			0.288		0.081	8.42	4.04	0.146
Mitchel et al.[49]	Adult	14.84	17.2	38.4	3.66	34.9				13.32	5.84	

Thyroid.—About one-half of the total iodine of the body (adult) is to be found in this organ. No information is available on total body iodine content for growing individuals; however, the content of the thyroid gland has been the subject of considerable study. It is of interest that the human fetal gland is able to collect radioactive iodine by the fourteenth week of gestation, coinciding with the time of appearance of definite follicles in the thyroid area.[10] Palmer and associates[55] report results of iodine analyses of the thyroids of eighteen late fetuses and newborn infants at an average value of 25 mg. per 100 grams dry weight, but the range of values was rather large. Twenty per cent of the total iodine was in the form of thyroxine. Leland and Foster[41] analyzed fifty-two adult glands, finding an average value of 174 ± 66 mg. per 100 grams. Subjects in both series were presumably from the New York City area. Although the total concentration in the adult gland was of the order of seven times that found in the newborn, the per cent of total iodine as thyroxine was approximately the same (25 per cent). Widdowson and Spray[77] have recently published a series of observations on thyroid iodine content in subjects ranging from the young fetus to the adult. The specimens were collected in England. The results are in terms of fresh weight and therefore cannot be directly compared to those cited above. (Table VI.) Average iodine content shows an increase with each successive age group, yet the range of variation is so large that there

TABLE VI. TOTAL IODINE CONTENT OF THYROID GLAND AT VARIOUS AGES

NO.	AGE	IODINE, MG./100 GM. FRESH TISSUE	
		AVERAGE	RANGE
6	280-910 gram fetus	2.4	0.5- 6.0
8	1,700-4,400 gram fetus	3.1	0.3- 8.0
5	Newborn	6.5	0.3-14.0
11	15 da.-7 mo.	8.4	2.7-18.0
6	1-4 yr.	15.3	2.0-39.0
4	5-12 yr.	25.0	13.0-38.0
3	21-31 yr.	41.7	27.0-58.0

is considerable overlapping. The period of most rapid increase is seen to occur during middle childhood.

Serum protein-bound iodine progressively falls during infancy[14]; yet total blood iodine shows no consistent age variation.[19] Basal metabolic rate also declines. Correlation of total body mass with thyroid iodine content would seem to be impossible since the total amount of iodine in the adult gland is of the order of 100 times that of the newborn infant, while the body weight ratio is 20/1. The total metabolism of the adult, i.e., caloric expenditure, is about six or seven times that of the young infant. Perhaps the increased amount of thyroidal iodine in the adult is due to greater storage. The placenta is permeable to thyroxine, so that the 4/1 ratio of total iodine to thyroxine iodine, noted to be identical in the newborn infant and adult, may merely reflect the situation in the mother. It would be of interest to study this ratio during later infancy and childhood.

Liver.—There have been a number of studies relating liver composition to age, particularly with regard to elements essential for hematopoiesis. I was unable to find any reports dealing with electrolyte composition. Unfortunately, the studies all suffer from the objection that most of the specimens were taken, at autopsy, from subjects dying of acute or chronic disease. Although the cause of death is noted in most reports, little if any information is given relative to nutritional status, hemoglobin levels, or therapy with iron and transfusions.

Widdowson and Spray[77] state that the liver and spleen of the newborn infant contain approximately 13 per cent of the total body content of *inorganic* iron, 55 per cent of the copper, and 29 per cent of the zinc. These values are fairly constant throughout the latter half of fetal life. In the one adult subject dying accidentally these two organs contained only 1½ per cent of the total body inorganic iron, 5 per cent of the copper, and 7 per cent of the zinc.[76]

Ramage and co-workers[58] carried out spectrographic analyses of the livers from 111 subjects for *inorganic* iron, copper, manganese, rubidium, and calcium. The subjects ranged in age from the late fetus to children 12 years old; only one of the postnatal subjects died of accidental causes. Results for iron (nonhemin) and copper are illustrated in Figs. 8 and 9. Iron content during fetal life averages 0.2 to 0.25 per cent of dry weight, rises to a maximum of 0.37 per cent during the first two months of postnatal life, then drops precipitously to 0.15 per cent in the latter half of the first year. The low point (0.05 per cent) is reached during the second and third years of life, whereupon the concentration rises very gradually to an average value of 0.09 per cent in late childhood. Copper content tends to parallel the curve described by iron, the ratio between the two being fairly steady at about 1/10 except that the low value for copper noted in late infancy tends to be maintained throughout latter childhood. The rise in liver iron concentration shortly after birth is undoubtedly related to neonatal blood destruction, and it is of interest that the curve shows some similarity to that for blood hemoglobin concentration. The total amount (not concentration) of inorganic iron in the liver, following the initial infantile drop, does not regain the birth value until the fifth year of life.

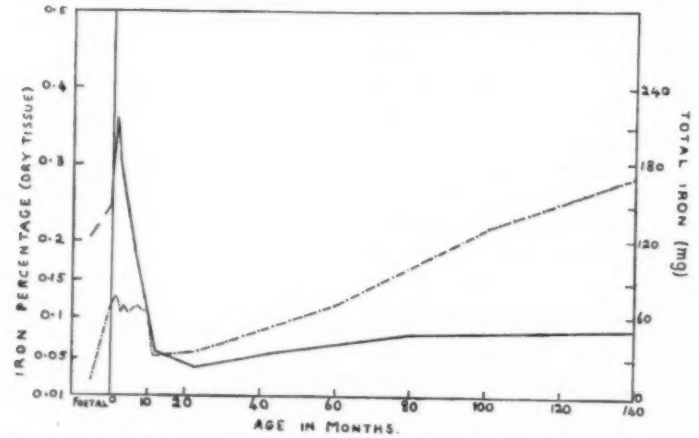

Fig. 8.—Changes in liver inorganic iron with age. ———, Iron per cent; –.–.–, total iron. (Reproduced from Ramage, Sheldon, and Sheldon; Proc. Roy. Soc., London, s.B **113**: 308, 1933.)

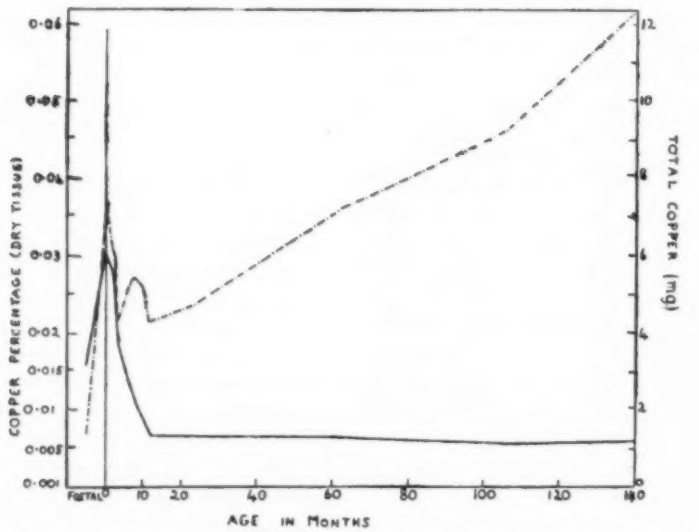

Fig. 9.—Changes in copper content of liver with age. ———, Copper per cent; –.–.–, total copper. (Reproduced from Ramage, Sheldon, and Sheldon: Proc. Roy. Soc., London, s.B **113**: 308, 1933.)

Curves for liver iron and copper roughly comparable to those presented above have been obtained by Widdowson and collaborators,[76] who noted that the minimal concentration occurring late in infancy was about one-half to one-fifth that of the newborn value on a fresh weight basis. This same general trend has been noted by Ashby,[2] and by Brückmann and Zondek[6] who studied a series of Palestinian subjects. The latter authors also presented data for inorganic iron and copper of the *kidney:* although copper content showed no consistent age variation (average—26 mg. per kilogram dry tissue), iron tended to follow the same general course exhibited in the liver with an average maximal value of 0.02 per cent at birth, a minimum of 0.008 per cent at 1½ to 3 years of age, and a gradual rise to 0.017 per cent in the adult (dry weight basis). Gladstone's[28] series of liver analyses on subjects living in this country confirms the age changes noted above with regard to iron.

Modern infant feeding practices appear to have had little influence on the over-all picture of the chemical growth of liver, data collected from periods as widely separated as 1912 (Ashby) and 1951 (Widdowson) showing only minor differences.

Manganese determinations were reported in two series of investigations. Ramage and co-workers[58] noted a marked rise in manganese concentration of the liver from a "trace" in late fetal life to a level of 0.009 per cent (dry weight basis) at birth. Due to the small amount of manganese present in milk, this value drops abruptly to roughly one-half this during the first two months, birth values being regained by the age of one year. Thereafter manganese concentration remains fairly constant. On the other hand, Brückmann and Zondek[6] found that manganese concentration showed relatively little age variation.

Widdowson and Spray[77] report the only existing series of zinc determinations. In terms of fresh weight, zinc concentration in the liver varies from 3.5 to 9.2 mg. per 100 grams and shows no tendency to vary with age.

According to Ramage and associates,[58] rubidium and calcium concentrations both show considerable variability but no consistent age variation. The range for rubidium (0.0027 to 0.0046 per cent of dry weight) was much less than that for calcium (0.03 to 0.24 per cent); it is stated that the former tends to parallel potassium but no figures are given for this element.

Ellison and Moore[18] reported on the vitamin A content of 106 livers representing a wide age range, and summarized data obtained by other groups of workers. With the exception of the newborn infants and the adults, in whom death occurred accidentally, the vast majority of the subjects studied suffered from acute or chronic infections. Mean values are low in infancy, ranging between 27 and 37 International Units per gram. At about 4 months of age, vitamin A concentration abruptly rises to between 100 and 150 I.U. per gram, after which the rise is more gradual to culminate in the average adult level of 290 I.U. per gram. Since infections serve to deplete vitamin A stores,[11] the fact that the adult specimens alone were taken exclusively from subjects dying accidentally may have made the age curve somewhat steeper than it actually is. Clausen[11] notes the importance of the liver in vitamin A economy, stating

that about two-thirds of the total body content of the adult and 90 per cent of that of the infant is to be found in this organ. The age curve for serum vitamin A and carotene very nearly duplicates that of liver vitamin A concentration. According to May and coworkers,[45] serum vitamin A levels show an abrupt rise at 5 to 9 months of age with carotene exhibiting a somewhat more gradual increase at about the same time. It is also of interest that the vitamin A content of body fat increases with age.[11]

TABLE VII. MUSCLE COMPOSITION AT VARIOUS AGES*

AGE	WATER (%)	N (%)	Cl (MEQ./KG.)
Newborn (premature)	86.1	1.90	49.4
10 da.	83.9	2.08	34.7
1 mo.	81.2	2.24	35.2
30 yr.	74.4	3.04	16.9
54 yr.	74.6	3.07	18.6

*Values in terms of fresh tissue.

Muscle.—The importance of this organ in the general electrolyte economy of the body is well understood, yet there is surprisingly little data available in the literature on the matter of compositional changes during growth. Kerpel-Fronius[37] has presented the following series of analyses of human muscle (Table VII). Water and chloride content both decline and nitrogen content increases as growth proceeds. Using Klose's[38] values for the newborn infant and Shohl's[62] for the adult, comparison of muscle composition between the two on a fat-free basis is as follows: the newborn to adult ratios are 1.8 for Na, 0.6 for K, 1.4 for Cl, 1.0 for Mg, and 1.2 for P. The analyses upon which these values are based were done many years ago (for instance, Shohl relied in large part on Katz's results dating from 1896), so that we may look upon Kerpel-Fronius' more modern figures for chloride as probably more indicative of the true state of affairs. The latter indicate that newborn-adult chloride ratio is about 2.0/1. The greater chloride content of newborn muscle is almost exactly offset by the much larger relative muscle mass of the adult, so that this organ embraces about 10 to 11 per cent of the total body extracellular fluid at both ages.

Brain.—More data is available on chemical changes accompanying growth for this tissue than for any other single organ. Thudichum began his chemical study of the brain in 1865. In 1919, MacArthur and Doisy[43] reported results obtained on brains taken from subjects of varying ages. More recently Page[54] has summarized the existing data on the chemical composition of this organ, including age changes, in his book *Chemistry of the Brain.* Not only has mineral composition been studied, but the chemical investigations have included detailed analyses of lipid, protein, and vitamin components as well. Consequently, our information on chemical growth of the brain is exceptionally complete. Fortunately for the analyst, the brain is in the unique position of enjoying a relatively protected position in the electrolyte cycle; in contrast to muscle, for example, it remains but little affected by disease processes which result in states of over- or underhydration. None of the brain lipids is in the form of neutral fat; the use of fat-free tissue weight as a basis for comparison is therefore impractical. Phospholipids make up about one-half of the total lipids of the brain, which in turn comprise a sizeable fraction of the total solids of this organ. Next to the

adrenal, brain tissue has the highest cholesterol and ascorbic acid content of any tissue in the body.

Fig. 10 illustrates changes in water and lipid content of the brain, as compiled from several sources. Water content drops rapidly during the period of late intrauterine life and infancy and then more slowly in later childhood. Total lipid values, expressed in terms of per cent total brain solids, follow a curve which is practically a mirror image of that for water. Most of the lipid fractions follow this same course so that the relative proportions of phospholipid and cholesterol do not change greatly during growth. Cerebrosides, which are complex lipids built up by combining galactose, a fatty acid, and a nitrogenous base (sphingosine), behave somewhat differently. MacArthur and Doisy noted that these substances could not be found in brain tissue until about the time of birth, following which there was a rapid increase in concentration.* These authors state that the increasing amounts of cerebrosides laid down in early infancy are probably concerned with the morphologic process of myelination. Analytical methods for cerebrosides are not specific, however, so no more than general conclusions are possible.

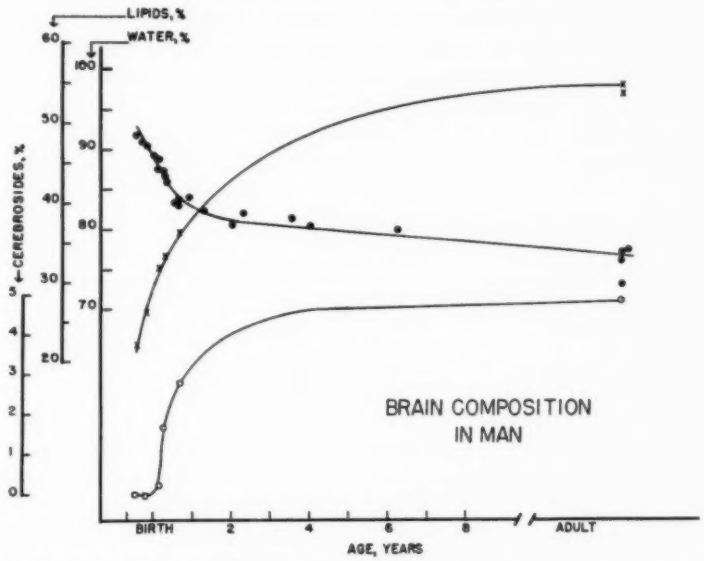

Fig. 10.—Changes in brain composition with age. Data of MacArthur and Doisy,[48] Cohn,[12] and Koch and Mann.[40] Values for lipids and cerebrosides are in per cent total brain solids.

Values in Fig. 10 are for whole brain substance. Through a study of various portions of the brain, MacArthur and Doisy found that as development proceeds, the brain stem differentiates chemically at a more rapid rate than the forebrain.

Table VIII attempts to summarize a variety of data on brain composition

*Cerebrosides have been implicated in only one disease. Large amounts of kerasin are found in the liver and spleen of patients suffering from Gaucher's disease.

at various ages. Ergosterol content drops rapidly at the time of greatest somatic bone formation. Copper content roughly parallels the curve of copper concentration for liver and kidney. The sharp drop in vitamin C content of cerebral and cerebellar cortex stands in contrast to the relative lack of change in spinal cord; this may possibly indicate a decline in cortical tissue metabolism with age. The vitamin C content of cerebrospinal fluid and pituitary also declines as growth proceeds. It would be of interest to attempt to correlate changes in alpha rhythm in the electroencephalogram (the wave frequency gradually speeds up during childhood) with some aspect of chemical composition.

TABLE VIII. CHANGES IN BRAIN COMPOSITION WITH AGE

AGE RANGE	FRESH WEIGHT			MG. % DRY WEIGHT	
	ERGOSTEROL* (MG. %)	ASCORBIC ACID† (MG. %)			
		CORTEX	SPINAL CORD	COPPER‡	CALCIUM§
Fetus	36-65	65	16	--	63
Newborn	20	--	--	1.5-2.0	52
0-9 mo.	13-32	23	17	0.6	23-28
1-2 yr.	3-5	--	--	1.4	19-24
3-8 yr.	--	18	16	--	18-20
Adult	11	10	13	5.0	17

*Data of Page.[34]
†Data of Plaut and Bülow.[37]
‡Data of Brückmann and Zondek.[6]
§Data of Cohn.[12]

DISCUSSION

Space will not permit a discussion of the changes in serum and whole blood composition accompanying growth. It is well known, of course, that quantitative alterations in acid-base equilibria, serum protein-bound iodine, protein, phosphorus, and the like occur during infancy and childhood. Hemoglobin, for example, undergoes qualitative changes as well. Growth changes in the excretion of creatine and certain of the hormones have also been studied. Certainly a discussion of these aspects of chemical growth would seem to be warranted at some future date.

Infancy and childhood is a period of chemical as well as physical and emotional maturation. This review, in summarizing many of the features of chemical growth, has, I hope, made clear the gaps in our present-day knowledge of this facet of the general growth process. These pages have been devoted to descriptive rather than etiological phases of chemical growth. Synthesis can only follow accumulation of observational data, and our knowledge of this field is far from complete. Changes in chemical composition occur in all mammalian species. To pose just a few questions: In what way does chemical growth in the human being, unique among mammals in possessing a long preadolescent growth phase, differ from that exhibited by lower animals? What constitutes optimum growth in man? And can the answer here be found in terms of chemical composition rather than mass proportions?

Moulton's announcement of the concept of "chemical maturity" was one of the first attempts at synthesis in this field. He defined "maturity" as that point in the life cycle which marks the dividing line between the phase of rapid change in chemical composition

and that of more gradual change. When the fat-free composition was plotted against age for a number of species the biphasic character of the resultant curve was clearly apparent in all instances. Curves depicted in his article are of the same general type as illustrated in Figs. 1, 2, and 10 in which the period of infancy marks the phase of most rapid change in chemical composition. "If the age at which chemical maturity is reached is divided by the length of life—both expressed in days of conceptional age—and the results expressed as percentages, a fairly constant figure is obtained. . . . It is sufficiently constant [in all species so far studied, including man] to permit the formulation of the following tentative law: That mammals reach chemical maturity at different ages, but these ages are a fairly constant relative part of the total life cycle."[51] Moulton found the average value to be 4.4 per cent of the total life span; for man this was calculated to be 1,280 days posteonception, or at about 3 years of age. Although it may be a coincidence, this happens to be the period in childhood which marks the end of the phase of infantile deceleration in over-all growth rate, the point at which growth is minimal. *Specific growth rate* is also minimal at this particular time.

Moulton assumed that the human being of 3 years was chemically "mature" because changes in composition following that period of life were quite small in comparison to those occurring before then. However, subsequent changes do occur, and the logarithmic method of plotting chemical growth, illustrated in Fig. 3, emphasizes clearly that *percentage* change in composition remains the same throughout growth. As noted previously, specific growth rates are much higher in infancy than later on. The time factor is at the crux of the situation: when this is circumvented by the double logarithmic plots, it becomes apparent that a change in mass from 1 to 10 kilograms involves about the same degree of alteration in chemical composition as a change from 10 to 100 kilograms. Since the former involves a much shorter period of time than the latter, time plots will naturally reveal that the curve is much steeper in early life.

Obviously, the general growth plan embraces far more than mere additions to existing tissue mass. The data reviewed here, and particularly those discussed under total body water, sodium, potassium, and chloride, lend emphasis to the idea that a tissue does not reproduce an exact replica of itself as it grows, but rather that each bit of new tissue laid down differs from its predecessors. Viewed from the concept of differential growth ratios, this changing pattern of tissue composition is a *continuous*, predictable, and systematic one. Tissue components evolve in constant percentage increments: whenever total growth (i.e., specific growth) is rapid, so, too, is the *change* in composition rapid. Infancy is therefore a period of profound change and brilliant accomplishment from the standpoint of chemical growth.

Further, Medawar[47] concludes that "the curve of specific growth suggests that the energies of growth decline progressively; that living matter progressively loses a power to multiply itself at the rate at which it was formed." Organisms age fastest when they are young. Could not the geriatrists apply the lessons to be learned from the study of chemical

growth toward a better understanding of the ageing process?

Yet another concept of the processes involved in chemical growth has been put forward by Lowry and Hastings.[42] They have suggested, on the basis of calculations from analytical data, that "growth in tissues [is associated] with a relative increase in the proportion of cells, and a resultant decrease in the amount of extra-cellular fluid, with little sign, thus far, of marked alteration in the composition of the intracellular or extra-cellular phases. . . . It would seem of practical advantage to make increasing use of histochemistry in growth studies to distinguish real changes in cell composition from apparent variations due to changing proportions of cells. By this means it should be possible to obtain a more intimate picture of the quantitative developments which take place in the growing organism."

A glance at the bibliography should convince the reader of the debt owed to the early workers, in particular the Germans of four to six decades ago, in the field of chemical growth. Modern refinements in analytical techniques, such as the flame photometer, and the matter of avoiding mineral losses during tissue ashing procedures, should serve as an incentive to stimulate further work in this field.

Perhaps the most pressing need for the future is the study of the maturation of enzyme systems. The prerequisite of fresh tissue for enzyme determinations renders such studies most difficult in man. Application of modern techniques to animal tissues at various phases of the growth cycle would permit the formulation of hypotheses concerning enzymatic "growth" in man and point the way toward the most efficient method of attacking this important problem. The recent demonstration of the presence of a "growth curve" for glutamic acid decarboxylase in mouse brain is a case in point.[59] The red blood cell constitutes a readily available tissue for study, and information on age variations for one of its enzymes, carbonic anhydrase, is now in the literature.

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Psychologic Aspects of Pediatrics

EVERYDAY PROBLEMS OF THE PRESCHOOL CHILD

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MANY parents have the notion that the normal child is without problems. The stress in current psychiatry upon the fact that many neurotic problems are the outgrowth of early human relationships in the family has been translated to mean that a parent should feel guilty every time *his* child has a problem. This, of course, is not true. Every child has problems—being alive at all presents certain difficulties and conflicts that are bound to emerge from time to time in so-called "problem" behavior. The baby who wears himself out standing and holding on to his play-pen rail because he does not yet know how to sit down gracefully has a specific problem that no amount of parental understanding can avoid. The baby may get angry and scream again and again before he finds that he can let himself down as well as pull himself up. In the meantime he shows "problem" behavior.

Many of the "problems" of early childhood are off-shoots of some quite natural developmental difficulty. They do not inevitably prophesy profound emotional disturbances all through life. If parents comprehend that *all* children have some problems, they would be more relaxed and happier with their own children. And relaxation and happiness invariably help the child through his difficulties with a minimum of injury.

Another false notion sometimes fostered by a superficial knowledge of child development or psychology is that all parents should behave in the same way, that there is some "correct" thing to do—or even to say—on all occasions. But parents are just as much individuals as their children. Expectations for children vary from family to family—and they should. One mother will be quite undisturbed when the children mess up the living room with their play. She feels that they need a change of scene, and it does not annoy her to help them clean it up after a play session.

Another mother objects to having the children in the living room. It irritates and upsets her to seek marks on her cherished furniture. Why shouldn't each mother set up her own standard in matters of this kind and stick to it? The important thing is not to be just like one's neighbor, but to be consistent with oneself.

Sometimes the profusion of new knowledge concerning the mental and emotional development of children, and the rapid switches that have taken place in the past twenty years (for instance, from rigid feeding schedules to virtually none at all) have a paralyzing effect upon parents. I once heard it seriously argued by a professional therapist that a 3-year-old who wants a Martini with his parents might feel rejected if he were refused it. I have also heard it suggested with equal seriousness that pulling loose a button off a small boy's coat in order to salvage the button may stimulate castration fears.

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If such extreme theories were correct, parents would be amply justified in feeling concerned about every act and every word, no matter how apparently trivial. The reassuring fact is, however, that soberer minds in all schools of psychiatry and child development are in agreement that the child who has a background of steady affection and kindly discipline is not likely to be traumatized by a casual word. Moreover a great deal of present-day theory is still not adequately tested clinically. When a hypothesis does not stand the test of time and experience, it must be altered until it does. We see this happening in the physical sciences, and it certainly is not unreasonable to suppose that it must happen in all other fields as well. I will not venture to predict what the state of the psychologic sciences will be in the year 2000, but it will certainly not be a simple repetition of the theories of 1952.

It is with these reservations that some of the more common behavior problems of the preschool years are discussed.

THE BEGINNING OF NURSERY SCHOOL

The first weeks at nursery school are often a time of stress for both child and parent. Today, when children often begin their school lives while hardly more than babies, this is a common problem.

Leaving his familiar home setup and being separated from his mother make the beginning of school a major event in the child's life. The majority of youngsters are so delighted by the presence of other children and by the wide variety of play materials that they make the transition easily. But others cling to their parents in doubt and fear.

Individuals vary widely in the age at which they are ready for school. Some youngsters are ready—even eager—by the time they are 2. Others are not yet ready at 4. But the fact that the child resists school does not always mean that he is better off at home. The overdependent child will never be ready to drop the apron strings easily. It is to his ultimate gain to become a member of a larger group than his family during the years when his personality is still malleable.

Some of these children cling desperately to their mothers for the first two or three weeks of school. Then their healthy interest in the activity around them helps them to become members of the group almost in spite of themselves. A warm relationship with a teacher, a genuine friendship with one other child may be the foundation upon which a hesitant child builds a feeling of "at-homeness" in school.

But other children are more dependent or more aloof. For them the school remains an alien place, and they are miserable for months. They may not be ready to live in a group for even a part of the time.

The reasons why they resist school and are unhappy there are numerous. A few common ones are jealousy of a new baby at home, the suspicion that they are being pushed out because they are not wanted, a pervading anxiety in any new situation. Such children may need time to work out their home problems before taking on new ones. In some cases this decision is better made with the help of a guidance counselor or child psychiatrist.

In other cases the problem of adjustment to school is obviously more the mother's than the child's. As soon as the child has settled happily down to

work, the attention-seeking mother dashes to him to say, "Darling, I'm leaving. Don't cry. Kiss mother." The effect of the scene is to make the child cling to his mother tearfully, and the mother is satisfied that her child loves her and needs her desperately. A tactful teacher may help at this point.

Many teachers, incidentally, make a point of visiting the home before school starts. The child has the advantage of meeting her for the first time in familiar surroundings—and often this casual contact is a real strength to him in the first strange and sometimes lonely days of school.

For most children, however, the easy informal atmosphere of a good nursery school is a pleasant transition from home to life outside of home. The emphasis upon personality development rather than on content means that here a child may get important help from sympathetic adults other than his parents. He may live a healthy social life with a consistent group of children. He learns the simple rules of sharing. He finds that he cannot remain the center of attention in a group of active children. For the most part the "lessons" of nursery school are steps forward toward healthy independence and maturity.

FEEDING PROBLEMS

Feeding problems, though perhaps not so widespread as they were twenty years ago, are still common. Too many children sit before their balanced meals, resistant or just uninterested. The ironic fact is that many mothers who know just what to feed their children cannot get them to eat it.

In fact, no children will turn into a rickety weakling because of an occasional lapse from an ideal diet. Yet many mothers become anxious when a child refuses an egg for two days in succession because the diet list says he should have one every day.

There is not better way to create a first-class feeding problem than to make mealtime a period of tension. It will not be long before the child, consciously or more likely unconsciously, uses mealtime as a chance to get attention, to play on his mother's obvious anxiety, and to emerge victorious.

Adults should remember—and be frequently reminded—that in feeding a child they must rely on his own healthy instincts. A 3-year-old cannot read diet lists but he can feel hunger. It is his own biologic need that makes him eat—not any grown-up propaganda that spinach is good for him and that mother wants him to eat it. No normal healthy adult weighs and measures his own portion of lunch and says, "I must get this down whether I like it or not." It is quite as ridiculous to expect to feed a child with mathematical precision.

Moreover, it has been shown that the appetite of a healthy child is a safe guide for him and his family. Dr. Clara Davis, in her studies on free choice of diet in children, found that what appeared to be an unbalanced diet day by day turned out to be a sound diet when a longer interval, such as a month, was chosen. A child is a going concern, and he does not need to "balance" every afternoon any more than a corporation expects to balance its books at closing time every day.

Parents often need to be reminded that the child's growth rate falls off sharply at the end of the first year. That means that the preschool child needs less food in proportion to his

weight than does his baby sister, who is still growing at top speed. To reduce the whole thing to an absurdity —if a baby who weighed 8 pounds at birth, and 24 at one year, went on growing at the same speed he would weigh over 200 pounds by his third birthday!

Another fact to keep in mind about food is that the preschool child cannot be expected to have cosmopolitan tastes. He is likely to enjoy a few favorite foods and to resist any departure from them. Surely he may be allowed the simple pleasure of enjoying his favorite foods until he shows a spontaneous interest in others that appear at the grownups' table.

Another way to encourage appetite is to give the child himself a chance to help with his eating. This may be done much earlier than many adults realize. It is as natural for children to want to feed themselves as it is for them to want to eat; and it is to be expected that their first attempts will not be outstanding for neatness. But those attempts should be handled with sympathy and understanding. As soon as the baby can handle a spoon, he should be allowed to do so. The thrill of getting a bite or two into his mouth unassisted will go a long way toward interesting him in food and toward building good eating habits later on. Since self-feeding is likely to be a slow process, the mother can have another spoon and give her youngster a bite or two when his own efforts fail.

A sudden, arbitrary weaning may have a detrimental effect on a child's later appetite, and conversely, a peaceful gradual weaning will probably have a good one.

Although preventing a feeding problem is easier than curing one, that can be done too. And by the same method —a fundamental trust in the child's own need and desire to eat. A mother who believes in the soundness of her child's instincts will not get frightened or angry when her youngster goes on a temporary hunger strike. Nor will she make mealtime into a picnic in an effort to coax or bribe him into eating. She will make an effort to give her youngster appetizing food that is good for him. She will help feed him if he seems unable or unwilling to eat alone. She will allow a reasonable time—say twenty minutes or half an hour—and then she will remove the plate without excitement or anxiety. One device that often helps with the child who has a feeding problem is to serve small portions for a time. The positive gesture of asking for more is far better than the negative one of turning from a too-full plate. Re-education takes time and patience—but the results make it worth while. Removing tension at mealtime will relax a child in other aspects of his life as well, so that the general family atmosphere will brighten up as a result.

MASTURBATION

Psychiatrists tell us that masturbation, rather than being a symptom of precocious or even perverted sexual awareness, as it was formerly thought to be, is a normal phase in the growth toward sexual maturity. Most children masturbate at one time or another. The young child's experimental attitude toward the world around him includes experiments with his own body, its sensitivities, its pleasures.

Yet in spite of this, many parents are upset when they find their own child handling his (or her) sex organs. No matter how enlightened they may

lic in theory, they have usually inherited a good many superstitions, among them the notion that masturbation is somehow both harmful and shameful.

It is true that excessive masturbation, like excessive thumb-sucking, may indicate uphappiness or tension. It, too, offers an easy retreat from outgoing social life and is a way of avoiding conflicts that are a part of emotional growth.

A child should not be shamed because of masturbating, nor should he be punished. It is also wise to remember that the parent's own feelings of shock or anxiety may be communicated in subtle ways—by a facial expression, by a tone of voice. Even without overt threats or punishment, it is possible to make a child feel severely guilty because of masturbation.

The only thing the adult can do is to offer the child a full and active play life with other children, and to give him the solid feeling of being loved and wanted that will make it unnecessary for him to satisfy his emotional and sensual needs by means of his own person.

TIMIDITY

Timidity or shyness is one of the "phases of growth" problems mentioned at the beginning of this article. Fear of strangers toward the end of the first year is normal. If we regard temporary shyness as the result of increasing awareness of people, we can see why the baby who used to enjoy being handed from one person to another now elects to remain with the one he knows best—his mother. During this period, his choice should be respected. A time will probably come when this withdrawal will be replaced by an eagerness to meet the visitors at the door and to engage them promptly in conversation.

Another normal kind of shyness is a tendency to withdrawal upon meeting other children in groups for the first time. Many preschool-age children need a warming-up period. After a few experiences, they learn to stick up for their own rights and to play actively with other children.

A persistent and unchanging timidity, on the other hand, may be a reflection of tensions in the preschool child's life. As so often happens in emotional problems, either of two extreme parental attitudes may cause the same result. The father, who is ashamed of his boy for being a "coward" and who makes a big issue of his not fighting back, will probably push the child into greater timidity. And at the other extreme, the mother who encourages a child to run to her every time he gets into difficulty, and who fights his battles for him, is also going to encourage greater timidity and dependence.

Not infrequently there two attitudes are found in the same family. The child exposed to such shifting attitudes feels not only inadequate, but confused as well. Positive measures for helping the timid child are: Mild praise for specific accomplishments such as a colorful painting, or a sturdy block-building; plenty of opportunity to play with other children with an intelligent adult on the scene (this is because the very timid child may be unable to get himself out of the corner he has backed into without adult assistance); and relaxed good times at home.

AGGRESSIVENESS

Early aggressiveness, like early shyness, is a normal phase in a child's social growth. At first, when a youngster

wants the pail and shovel that are being used by another, his impulse is the direct and primitive one of seizing it. The interest in the pail and shovel, the vigor that leads him to take steps to make it his own, are fine. The method of using them is not quite acceptable. But his impulses should be guided, not squelched.

Some early aggression is simply exploratory—a natural curiosity to find out if one's neighbor's cheek tastes as tempting as it looks, a curiosity about the physical qualities of long hair, eyes, ears, fingers, toes, and so on. It is only gradually, and with considerable adult help, that the preschool child learns that other children have feelings like his own, and that they, too, get hurt if he pinches or steps on them. He also learns only gradually that if he indulges in out-of-bounds activities, such as hitting or biting, he will be gently but firmly stopped. With the assistance of the grownups around him, he learns to appreciate the simple fairness of taking turns and he learns that it works out as well for him as for the other children.

When children are introduced early to social play and are handled in this simple repetitive, down-to-earth way, aggression rarely becomes a major problem. It is the child whose first aggressive moves were severely punished who is likely to persist in hurting other children needlessly. It is the child who feels pushed himself in psychologic as well as physical ways who wants to push others.

The aggressive child, like the shy one, needs plenty of opportunity for social life with children his own age. He needs to find out that sharing an idea or a toy can be as rewarding as grabbing or hitting. Often the aggressive child is actually fearful beneath his bold exterior. That means that he, too, like the shy child, needs to be handled with mild and friendly discipline. He needs to feel that he "belongs." Even though an understanding grownup may have to interfere to keep him from hurting his playmates, this can be done in a firm and friendly way, without drama or condemnation.

The aggressive child is often relaxed by vigorous muscular play. Clay, paints, hammer and nails, an open space where he can run at top speed, all of these may help him to work off the steam he generates in daily living. The aggressive child who is wisely handled may become a dynamic leader who makes a real contribution to group life.

JEALOUSY

One of the biggest crises in the life of a preschool child and his parents is the arrival of a second baby. Up to this time the older child has also been the only child, and he is bound to feel disappointment at having to share the spotlight with the new arrival. Some writers on child development imply that all problems connected with this normal jealousy may be eliminated by careful preparation before the younger child arrives. This is not so. Discussion of the fact that a new baby is on the way is all to the good, but, though it may lessen, it will not prevent jealousy.

Parents who are prepared for some hostility on the part of the older child to the new baby are far less disturbed by unfriendly words or actions than the parents who have somehow got the notion that it is possible to eliminate jealousy completely. For these latter parents every manifestation of jealousy is a sign that they have not

done a good job, either in preparing the older child, or in helping him to adjust to the new baby during the first months of his life. Their confusion and guilt usually paralyze them so that they are not able to exercise the friendly mild discipline that the older child needs when he attacks the younger one. Indeed some parents are so afraid of making the older child feel rejected that they make the younger one feel that way!

What can parents do to handle the problems of jealousy? First, a preparation a month or two ahead of the baby's arrival is advisable. The age of the older child should be the factor in the parent's decision about when to tell him about the new baby. A 2-year-old, with his hazy and unrealistic notion of time, will simply lose the significance of the announcement if it is made more than a few weeks before the birth. A 5-year-old, on the other hand, may be deeply interested in knowing that the baby is growing in his mother's body. His natural curiosity about where the baby is coming from will lead simply and easily to information about the beginnings of life.

It is fine if the older child can take a real part in the preparations for the new baby. He may go along on shopping trips for clothes and he may enjoy looking over the baby clothes already on hand. All of this will make the prospect more real to him. It is also wise to make any major shifts in routine before the baby arrives rather than during the process of adjustment. Attendence at nursery school, a change in the older child's room or his graduation from crib to bed, may seem either like the satisfactions that come with increasing maturity, or on the other hand, like the penalty one pays when one is unfortunate enough to have a small brother or sister.

Once the baby is on the scene it helps if the older child is given a small but genuine role in his care. It often worries grownups to see the cavalier fashion with which a 3-year-old holds a month-old infant, but actually the young one is not so breakable as he or she looks. And what small inconvenience this routine may be to the baby is more than cancelled out by the protectiveness it stirs up in the big child.

Parents have been warned time and again not to fuss unduly about the baby in the older child's presence. Fortunately young babies are content to be ignored except for physical needs during the first weeks of their lives. Usually these early weeks are no special problem. The baby is still a novelty and has not yet started to interfere with the older child's serious play interests. It is toward the end of the first year and during the second that jealousy usually rises to a peak.

At this point some children are overtly hostile. They wish loudly that the baby would go back where he came from. They do not hesitate to use force to detach him from a prized toy. This is normal behavior and should not cause the parents concern. Indeed, this frank jealousy is often the easiest to handle. All one needs is a consistent policy—a basic friendliness for the older child who is bothered by the baby, and calm, matter-of-fact checking of his violent attacks. If parents stop to think about the child's feelings, they will realize that the baby often *is* annoying, that the older child is frequently justified in his rage at having a handsome building pushed over or a prized doll torn apart.

Frequently, however, jealousy is not this direct. Some children practically ignore the baby, but make an out-and-out drive for increased parental attention. This may take forms that are unquestionably a nuisance to busy parents—bed-wetting, insistence on being fed, perhaps fears or tantrums that bring him dramatically into the limelight.

No matter what the behavior may be, it indicates the older child's anxiety about his status in the family. Usually the behavior itself ends with a patient and reassuring attitude on the part of the parents. One family inaugurated a special father-son story time in the evening. Another family invested in a baby-sitter two afternoons a week so that the mother and the 3-year-old could do some "grown-up" gadding about.

The child who is handled in a relaxed, consistent way will come to find out in time that being "big" provides as many satisfactions as being the baby. Parents cannot force a child to accept this point of view, but they can help him to discover the satisfactions of being the older brother for himself.

TANTRUMS

Practically all children have tantrums at one time or another during their preschool years. They require attention only when they occur with great frequency over a period of time.

There is little question but that the child in a tantrum would like to tackle his parent with the same violence that he tackles himself. But he is faced by a double danger. First of all, he is too small to win. And more important, he has a genuine fear that if he shows the extent of his (temporary) rage and hatred, his parents will stop loving him.

A temper tantrum is a rage reaction. It is a response to various kinds of outside pressure. One child will rebel against overstrict discipline and punishments. Another will respond to a series of petty interferences in his play by having a full-sized tantrum. I saw one 4-year-old, for instance, who was struggling to build a tall block structure. He was interrupted at least six times by the various adults in the family—his mother, his grandmother, his father, all wanting him to do something, to come and get his drops, to straighten his overall straps, and so on. Finally his mother appeared with a jacket for him to put on. At this point the child drew back, and knocked down a corner of his building. Whereupon he threw himself on the floor and screamed. His mother was astonished by the intensity of his reaction to what she considered a trivial matter. She had no idea how much previous interference the child had taken without protest.

The child who is constantly pressed to conform to standards that are beyond him and who is expected to be a credit to his family in everything he does is likely to resist without knowing exactly what he is fighting against. The overindulged child, whose parents take all of his problems away from him and who pursue him with attention, is also likely to have blind resentment against a world that stifles him and denies him the freedom to grow at his own pace.

Once tantrums have begun many parents feel that they must be stopped at all costs. In desperation they resort to spanking or other forms of punishment. Other parents are frightened

at the violence of the child's emotion and back down hastily before it. They may be afraid that the child will actually injure himself.

Neither the extremely harsh nor the extremely yielding reaction to a tantrum is necessary. It is quite safe to leave the child to work off his most violent feelings without fear of injury. When he is able to act rationally once more, the mother may want to sympathize with him—as in the case of the child who knocked over his block building. If the child's tantrum is staged where he can disturb other people, she may want to pick him up matter-of-factly and take him to a more isolated place. It is usually wise to stay with him until the storm has subsided.

She will also want to check up on her child's daily life to see where she is putting the pressure and whether it is excessive. She will try to keep him from getting overtired physically. She will allow him a good deal of leeway in such matters as choosing clothes, play materials, and anything else that is within his capacity. She will struggle to get him with other children whose needs and interests are similar to his.

FEARS

For every child who develops a fear, say of dogs because of an actual attack, there must be ten who develop the same fear without any basis in reality. Of course, many children pick up their parents' anxiety in the tone of voice, "Be careful of the doggie." But plenty of youngsters develop baseless fears. For instance, one little girl was terrified at the sound of people in the apartment upstairs. Even after going for a visit to see that they were quite unspectacular human beings, she would shiver and look apprehensive when she heard noises from above. Such fears are usually puzzling to adults, because they cannot be attached to any rational cause. Yet from a deeper point of view the fears have a logic of their own in the child's mind.

Actually the background for such irrational fear and panic is often similar to that of the child who has tantrums. Over and over again we find children who feel hostile toward their parents, and who are driven to conceal it even from themselves. The angry parent, in the child's imagination becomes a wicked witch, an angry beast, or a giant. By a transition of this kind the child is relieved of the necessity of admitting that he fears (and hates) his parents at certain times. We find that his apparently foolish fears make sense if we can see them through the distorting lenses of the child's own imagination.

The outside pressures which lead some children to explosive outbursts in tantrums may push other children into strange and unaccountable fears. Overstrict discipline, harsh punishments, rigidly high standards, overindulgence may be the background for various anxieties in the preschool years. In nearly every case, the child fears that his own hostility will cost him his parents' love. He needs, then, to be reassured by a change in handling where a parent has fallen into the errors mentioned above. At the same time he needs to be explicitly told that everyone feels angry at times, that his deep hidden feelings are neither dangerous nor unnatural.

RESISTANCE

One phase of development that puzzles and annoys parents begins when

their heretofore complaint baby learns how to say "No." Up to a certain point most babies seem literally unable to resist a pleasant suggestion. They "pat-a-cake" with gusto and behave in such a way that their parents believe that they have the most amiable baby in the world and that he will remain that way.

The extreme suggestibility of infancy is no sign of "goodness." It is simple immaturity, lack of awareness of self. A child who remained as suggestible as an infant would be far more of a problem to his family than the one who learns how to say "no," and to have ideas of his own.

The period of negativism coincides with the child's discovery of himself as a separate personality. At first, to judge by the evidence, little children do not differentiate between themselves and the world around them.

During this period the 2- or 3-year-old begins experimenting with refusals. He refuses to be washed or to go to the toilet. He may refuse his dinner, and he tries to escape when his mother comes to put him in bed. Indeed, refusal may become such a pattern that a child may shake his head no when he is offered seconds, but at the same time hold out his plate!

At this point many parents anxiously think that their child has become "bad." They begin on a strict regimen of discipline and punishments in an attempt to nip this pattern in the bud.

The trouble is that they nip too many buds. They forget that the child's resistance to authority contains the awkward beginnings of independence and initiative and healthy aggressiveness. The do-or-die approach may push a youngster into one of two extremes—timidity or indiscriminate rebellion.

By this I do not imply that the parent is merely passive during this period of resistance. It is up to him to teach the negativistic child that he may not refuse to go to bed, or to wash when he is dirty, that he may not play with such dangerous objects as scissors or knives or matches. But at the same time the wise parent will give his youngster considerable freedom in such matters as the choice of clothes or play materials. The child during these years is learning in what areas he is free and in what areas he is expected to conform to family rules. He cannot learn these things without patient guidance.

"BAD" LANGUAGE

The trial and error approach characteristic of young children almost invariably extends to language. Words generally reserved for the use of truck drivers with a flat tire somehow find their way into the vocabulary of the most tenderly reared preschool youngster.

The alert child is soon aware of the powerful weapon he has discovered. One child will use his bad language to horrify adults and, of course, to get immediate and excited attention. Another, particularly in the late preschool or early school years, will use his obscenities to increase his prestige with other children.

Bad language is not a serious problem unless it is combined with other symptoms of disturbance. It is almost entirely an attention-getting device, and the best treatment is to maintain an air of calm when a youngster uses the magic words.

Calmness may go along with a statement of rules about the use of "bad" words. They may be banned, for example, when Grandma is present because they are distasteful to her. Such a rule is based not upon a prissy or moral approach to words, but upon simple consideration for other people. Even a young child can understand this kind of reasoning.

Children whose ventures into profanity are treated in this relaxed manner are quicker to accept the local customs and family rules about language than are the ones whose lurid words are greeted by shocked attention or by amusement.

It is well to remember that childen often learn undesirable language from grownups!

DISCUSSION

These are all common problems that occur time and again in normal families. Unless they become acute enough so that special help is needed, they are handled best by stressing the positive aspects of the child's life. Briefly, we may stress the following aspects of healthy life and growth in the preschool years:

All children need a warm and flexible emotional relationship to their immediate families. They want to feel loved and wanted, and to give love in return. For the most part this affectionate relationship emerges spontaneously in the parents' care of the child.

Children need to know what is expected of them. They learn this through a kindly discipline that is not afraid to set limits to their activity. The child who is allowed to stand up on a car seat when he knows that the family rule is that he sit down is being exposed to psychologic as well as physical hazards. Only a dramatic procedure will convince him on future occasions that he is not the final authority in every decision that arises. The child who grows up without knowing a consistent discipline has a far harder time than the one who knows where he and his parents stand.

Children need plenty of opportunity for an active physical and social life. The child who struggles to make a block bridge is learning coordination and is getting good mental exercise in space relationships as well. The child who learns to take turns on a swing is learning social disciplines in an enjoyable way.

Children need opportunities for self-expression through materials of all kinds. When the aggressive child makes a rough human figure and then pounds it flat, he is expressing hostility in an acceptable way. When another youngster paints a picture of the ocean liner he saw on the river, he is pinning the experience in his memory and getting pleasure from the act of creating something that is beautiful to him.

A full and satisfying daily life is the child's best insurance against emotional difficulties now and in the future. He will have problems, of course, but they will be for the most part passing manifestations of some temporary or developmental difficulty. Most of these behavior problems do not respond to a head-on approach, but are changed more effectively by increasing the child's opportunity for the basic satisfactions mentioned in this summary.

Comments on Current Literature

BCG VACCINATION

EVER since the introduction of BCG vaccination a quarter of a century ago, there has been considerable difference of opinion as to the efficacy of the Calmette-Guérin vaccine in the prevention of primary tuberculosis. Difficulties encountered generally in attempts to carry out controlled investigations with the vaccine have made hazardous any conclusive statements concerning its true value. Recently, however, A. W. Dickie,[1] of the Royal Belfast Hospital for Sick Children, has reported a study which was carried out in the Pediatric Clinic of the Karolinska Institute, Stockholm, Sweden, where opportunity was afforded for following families in which some of the children had been vaccinated, and others in the family, for some reason, had missed being vaccinated.

During the period when Dr. Dickie was a Cow and Gate Travelling Scholar in Stockholm, he was able to analyze closely the records of a number of hospitals. He attempted an evaluation of the efficacy of BCG vaccine in families where the children were exposed to a confirmed case of active tuberculosis. He encountered families in which, for various reasons, some of the children had been vaccinated and others had not. Each family was scrutinized carefully as to the source of the tuberculous infection, the tuberculin reaction in all members of the family, the number of children who had received BCG vaccine, and those who had not, and for any other pertinent data. In sixteen families subjected to this type of analysis, there were twenty-two vaccinated and twenty-two nonvaccinated children. Of the twenty-two children who had not been vaccinated, twenty-one developed primary tuberculosis, while in the group of twenty-two children who had been vaccinated with BCG, only two showed any evidence of superinfection with the acid-fast bacillus.

The author feels that such a nonvaccinated group served very well as a control, and that the two groups could be compared legitimately in the source of infection, the regularity of exposure to the organism of tuberculosis, the social conditions of the families, general state of nutrition, racial susceptibility, et cetera. In this connection, Dickie points out that age is the most important primary factor, children under the age of 5 years showing a much more severe reaction to primary tuberculous infection than older children.

A very detailed study was possible of the incidence of tuberculosis among the children admitted to Norrtull's Hospital (Karolinska Institute) over the five-year period from 1945 through 1949. During this five-year period, 1,352 vaccinated children and 7,279 nonvaccinated children were admitted to the hospital. Twenty-six, or 1.9 per cent, of the vaccinated children had tuberculosis, as compared with 599, or 8.2 per cent, among the nonvaccinated children admitted during this period. Twenty-eight cases of tuberculous meningitis and (or) miliary tuberculosis occurred in the nonvaccinated group, and none in the vaccinated group. As the author points out, these findings are of interest, although the figures apply only to hospital admissions and in no way are to be considered representative of the children of Stockholm in general.

So far as human studies in tuberculosis are concerned, this one at the Karolinska Institute appears to have been carried out under unusually well-controlled conditions. The overall results of this study seem to indicate that BCG vaccine, when used properly, offers significant protection against primary tuberculous infection, particularly in the younger age group.

RUSSELL J. BLATTNER.

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News and Notes

Dr. J. H. Mason Knox, Jr., of Baltimore, one of the pioneer leaders in the field of child health, died in May, 1952, at the age of 79. For many years he was Chief of the Bureau of Child Health in Maryland which was established in 1922. He was the first president of the American Association for the Study and Prevention of Infant Mortality which was founded in 1907, and which later became the American Child Health Association. In 1926 he was president of the American Pediatric Society. He was a member of the staff of the Johns Hopkins Hospital for many years and a lecturer on child hygiene at the Hopkins School of Hygiene and Public Health. He made numerous contributions in the field of maternal and child health.

Dr. Samuel W. Clausen, professor of pediatrics at the University of Rochester School of Medicine, and pediatrician to the Strong Memorial Hospital, has been awarded the Kaiser Medal of the Rochester Academy of Medicine for his achievements as a "scholar, clinician and extraordinary teacher of pediatrics."

At the annual meeting of the **Section on Pediatrics** of the **American Medical Association** in Chicago in June, Dr. Eugene T. McEnery of Chicago was elected chairman for 1952-1953, and Dr. Wyman C. C. Cole, 3001 W. Grand Bldg., Detroit 2, secretary.

The **Jacobi Fund** of the **Section on Pediatrics of the American Medical Association** received $1,696 from 282 contributors according to the report made at the June meeting in Chicago by Dr. Hugh L. Dwyer, Custodian. Net income from investments was $188.76, and expense and distribution to essayists, $731.80. Trust value May 30, 1952, $6,890.04.

A symposium on the Metabolism of Potassium, sponsored by the M and R Laboratories, Inc., Columbus, Ohio, will be held at the **University of Minnesota,** Sept. 22, 23, and 24, 1952, with Dr. Irvine McQuarrie as chairman. A partial list of the participants includes: Dr. Allan M. Butler, Dr. Daniel C. Darrow, Dr. Richard H. Follis, Dr. George M. Guest, and Dr. John P. Peters. Living quarters will be available at moderate cost in the dormitories of the University. Members of the medical and allied professions are invited. There will be no tuition fee. For further information, write to the Director of Continuation Medical Education, University of Minnesota Hospitals, Minneapolis 14, Minn.

The **Le Bonheur Children's Hospital,** Memphis, Tenn., was opened June 15, 1952. The Medical Staff of the hospital, which is an open one, is organized, with the following officers: Dr. F. Thomas Mitchell, Chief of Staff; Dr. James G. Hughes, Vice-President; Dr. C. Barton Etter, Secretary; Dr. J. Spencer Speed, Chief of Surgery; Dr. J. A. Danciger, Chief of Medicine. The hospital will care for private and charity patients, white and Negro, from prematurity to 14 years of age, and has 110 beds.

On June 25 and 26, 1952, a Seminar was held, sponsored jointly by the Medical Staff of the Le Bonheur Hospital and the faculty of the Division of Pediatrics of the University of Tennessee, College of Medicine. The following speakers appeared on the program: Drs. Lenox D. Baker, Durham, N. C.; John Caffey, New York; Amos Christie, Nashville, Tenn.; Harold W. Dargeon, New York; Julius H. Hess, Chicago, Ill.

A preliminary report was issued in June by the thirteen research centers which have combined for the International Study of Rheumatic Fever. Since January, 1951, 658 patients have been admitted to the centers and the report is based on results in the first 302 cases. The report states that although individual symptoms may appear to be affected more favorably by one or another of the three drugs studied, ACTH, cortisone, and aspirin, no consistent pattern is evident which permits conclusions being drawn as to which is the most effective in controlling the illness in the acute stage. No report was issued on the comparative effectiveness of the three in preventing chronic heart disease.

Editor's Column

THE NEWER TESTS FOR POLIO

TWO recent developments in regard to poliomyelitis have made available exciting new tools for the investigation of the immunology of this disease, and provide promise at least of the practical diagnostic test that is so badly needed. These are the tissue culture serum neutralization test and the complement fixation test.

Prior to the development of these techniques the only methods available for the detection of antibodies to the poliomyelitis viruses were neutralization tests done in rodents or monkeys. Of the three serological types of poliomyelitis virus so far recognized, antibodies against only one (i.e., Lansing or type 2) could be determined in mice. Antibodies against the other two (Brunhilde or type 1 and Leon or type 3), which appear to be the cause of most of the recognized cases of paralytic disease, could be determined only in monkeys. Thus, the number of tests that could be done was limited when twenty or more monkeys were required to determine the antibody response of a single patient.

Enders and associates[1, 2, 3] demonstrated that the poliomyelitis virus could be grown readily in cultures of various human tissues and that degeneration of the cells occurred much more rapidly in cultures infected with virus than in control uninfected cultures. Cell destruction could be detected by comparatively simple methods and could be used as a criterion of growth of virus in the culture. The addition of antiserum was found specifically to inhibit this cell degeneration. Thus, tissue cultures might be employed instead of experimental animals for the isolation and typing of viruses and for the determination of neutralizing antibodies. The finding by Syverton, Sherer, and Butorac[4] and Smith, Chambers, and Evans[5] that monkey tissues would also support the growth of poliomyelitis viruses increased the availability of tissue culture techniques. Workers in New Haven[6] and Pittsburgh[7] have described methods of titrating serum neutralizing antibodies to poliomyelitis virus in cultures of monkey testicular tissue. These tissue culture techniques, although not suitable for general use, are comparatively simple and inexpensive, and can be done in laboratories that are not equipped to work with monkeys.

Numerous attempts have been made to detect poliomyelitis antibodies by complement fixation, precipitin, or other in vitro serological methods. These were uniformly discouraging until Casals, Olitsky, and Anslow[8] demonstrated that specific complement fixation could be obtained with antigens prepared from the brains of young mice infected with type 2 (Lansing) virus which had been adapted to this host. More recently, Svedmyr, Enders, and Holloway[9] have described the preparation of antigens from infected tissue culture fluids.

These fluids were concentrated by a simple method of ultrafiltration, and antigens were obtained that gave specific complement fixation with type 1 and type 3 viruses as well as type 2. From the relatively small amount of data so far available it would appear that complement fixing antibody, like the neutralizing antibody, becomes detectable in the patient's serum early during the course of the disease. In contrast to neutralizing antibody, which persists for many years, that which fixes complement seems to disappear from the blood within about two years. It has also been found that in some cases complement fixing antibodies may appear to one or both of the heterologous strains of poliomyelitis virus as well as to the homologous one demonstrated to be present in the feces of the patient. This lack of specificity of the complement fixation test may limit, to some extent, its usefulness in determining the specific type of virus causing infection, but should furnish a means of establishing serologically that the patient has experienced infection with one of the poliomyelitis viruses. Further investigation will be necessary to establish whether or not the rise in heterologous antibody is due to an anamnestic response or, as seems more likely, due to an antigen common to the three serological types.

Although much remains to be done in order to determine the usefulness and practicability of these newer serological procedures there would seem to be little doubt that they will be of great value in the diagnosis of poliomyelitis infections, epidemiological investigation, and in assessing the results of any program of immunization that may be undertaken in the future.

F. C. ROBBINS.

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POLIOMYELITIS AND IMMUNIZATION

THE problem of the relationship of immunization procedures to the incidence of localization of paralysis from poliomyelitis was mentioned in an editorial in the July issue of the JOURNAL. Results of the conference* to consider this, held under the auspices of the Public Health Association, were commented on.

It is apparent that there exists a statistically detectable association between immunization procedures and the localization of paralysis from poliomyelitis, although its quantitative importance is not great. Although the data do not show that the incidence of poliomyelitis was increased, that is strongly implied by the fact that localization of paralysis was sometimes determined by the inoculation. In any case, an inevitable public awareness of this relationship, and the highly emotional reaction of the public in its fear of poliomyelitis may in some communities handicap our well-established and invaluable immunization programs.

The physician may decide to ignore this whole matter as quantitatively not important, but if he chooses to be able to reassure parents of his patients that all risks are avoided, due to his awareness of the problem, it is quite possible to organize a dependable immunization program that is theoretically as well as practically safe. If we accept the well-established beliefs that initiation of immunization may be at 3 months, that successive injections can be given at monthly intervals, and that there is a fairly dependable immunity to poliomyelitis up to the age of 6 months, then there is, of course, no reason to vary the usual program because of the new hint of risk of poliomyelitis, since the third injection will be given at the age of 5 or 6 months. However, the individual physician may have different criteria in regard to these points. Even with different ideas about immunity, it is quite possible to devise convenient and effective programs that avoid inoculations in the "polio" months. As a single example, for an illustration, if it is assumed that immunity to poliomyelitis is not dependable at 6 months but is so at 4 months, and that initiation of immunization still could be at 3 months, the following program would be quite practical and would offer little difficulty in organization to an office nurse:

MONTH OF BIRTH	AGE AT FIRST INJECTION	MONTH OF FIRST INJECTION	AGE AT SECOND INJECTION	MONTH OF SECOND INJECTION	AGE AT THIRD INJECTION	MONTH OF THIRD INJECTION
January	3 mo.	April	4 mo.	May	10 mo.	November
February	3 mo.	May	4 mo.	June	9 mo.	November
March	3 mo.	June	4 mo.	July	8 mo.	November
April	3 mo.	July	4 mo.	August	7 mo.	November
May	3 mo.	August	4 mo.	September	6 mo.	November

Other programs in accordance with the habits or ideas of individual physicians can be easily devised. By July it is evident whether there is going to be any important increase in poliomyelitis, and if none exists the pro-

*Public Health Reports 67: 495, 1952.

gram does not need to be pursued. It is, of course, easier for the private physician to make such adjustments than it would be for a Public Health or other government agency doing wholesale prophylaxis.

The booster "shots" are the ones which are most troublesome to avoid since they are given in older children when no natural immunity can be assumed, but certainly there is no theoretical reason for giving them at any particular month or year in a child's life, and it is therefore quite easy to avoid them in the early summer months or throughout the summer, if a poliomyelitis epidemic should be found to take place.

JAMES L. WILSON

CRIPPLED CHILDREN IN THE UNITED STATES

A RECENT booklet* describing services for crippled children in the United States prepared by the Children's Bureau gives some interesting estimates of the number of crippled children in the country. "Nobody knows for sure how many there are with physical handicaps."

500,000 have handicaps requiring orthopedic or plastic treatment.

500,000 have or have had rheumatic fever.

175,000 have cerebral palsy.

200,000 have epilepsy.

100,000 under 10 years are believed to have congenital syphilis.

1,000,000 are deaf or do not hear well.

4,000,000 are blind or have poor eyesight.

These are the "best estimates which the Children's Bureau can make at the present time."

*C. B. Folder No. 38, 1952, Federal Security Agency.